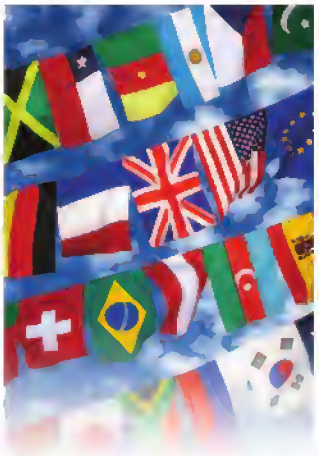

INTERNATIONAL PERSPECTIVES

Author Disclosure

Drs Klingenberg, Kaaresen, and Dahl have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/ investigative use of a commercial product/device.

Abbreviations

CoNS:	coagulase-negative staphylococci
CPAP:	continuous positive airway pressure
NICU:	neonatal intensive care unit
NIDCAP:	Newborn Individualized Developmental Care and Assessment Program
RCT:	randomized, controlled trial
UNN:	University Hospital of North Norway
VLBW:	very low birthweight

Neonatology Above the Arctic Circle

Claus Klingenberg, MD,* Per Ivar Kaaresen, MD,* Lauritz B. Dahl, MD*

Introduction

The Norwegian city of Tromsø is located 300 km north of the Arctic Circle at 69.7° N, the same latitude as the northernmost North American city, Barrow, in Alaska (Fig. 1). Often dubbed "the Gateway to the Arctic," Tromsø has played a central role in the history of arctic polar exploration. Many of the great explorers, including Nansen and Amundsen, set out from Tromsø for their dramatic expeditions in the late 19th and early 20th centuries. (1) Tromsø and the surrounding region has an arctic climate, with long winters and short summers. The sunset on November 20 marks the onset of the Arctic darkness (Fig. 2), which lasts until the sun rises over the horizon again on January 21. However, due to the Gulf Stream, the winters are not particularly cold in this coastal region. In the temperate summer, the midnight sun may be observed from May 21 to July 21. The rich fishing resources along the coast, today supplemented with modern aquaculture, are still a major source of income for people in this region of Norway.

Tromsø is the largest city in northern Norway, with 66,500 inhabitants, and hosts the northernmost University Hospital in the world. The catchment area of the neonatal service at the University Hospital of North Norway (UNN) is from the city of Narvik in the south to the Norwegian settlements on Svalbard in the north (Fig. 3). The area is located entirely above the Arctic Circle, comprises 23% (73,000 km^2) of Norway's total mainland area, and is sparsely populated with only 220,000 inhabitants (3.0 persons/km^2). There are five hospital-based maternity wards and three midwife-managed delivery units in the region. The neonatal intensive care unit (NICU) at UNN in Tromsø is the only level III neonatology service treating very low-birthweight (VLBW) infants and other infants in need of intensive care.

This article describes the establishment and current activity of neonatology in a sparsely populated region in the far north of Europe.

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Historical Background

During the 19th century, the scenic but sparsely populated coast of northern Norway was one of the poorest regions in Scandinavia. Although the Norwegian economy grew rapidly in the 1960s and 1970s, a continuous shortage of doctors proved to be a major obstacle for development of the health-care system of northern Norway. The establishment of the University of Tromsø with a medical school in 1972 improved the situation dramatically. When the Medical Birth Registry of Norway was established in 1967, the perinatal mortality in Norway, including northern Norway, was about 20 per 1,000. (2) Since 1970, perinatal mortality in Norway has gradually declined, reaching a level of 4 to 5 per 1,000 at the turn of the century. At present, the perinatal mortality in the arctic region of Norway is 5 per 1,000. (3)

The first pediatric hospital-based service in northern Norway was established in Tromsø in 1965. In those early years, there was no NICU

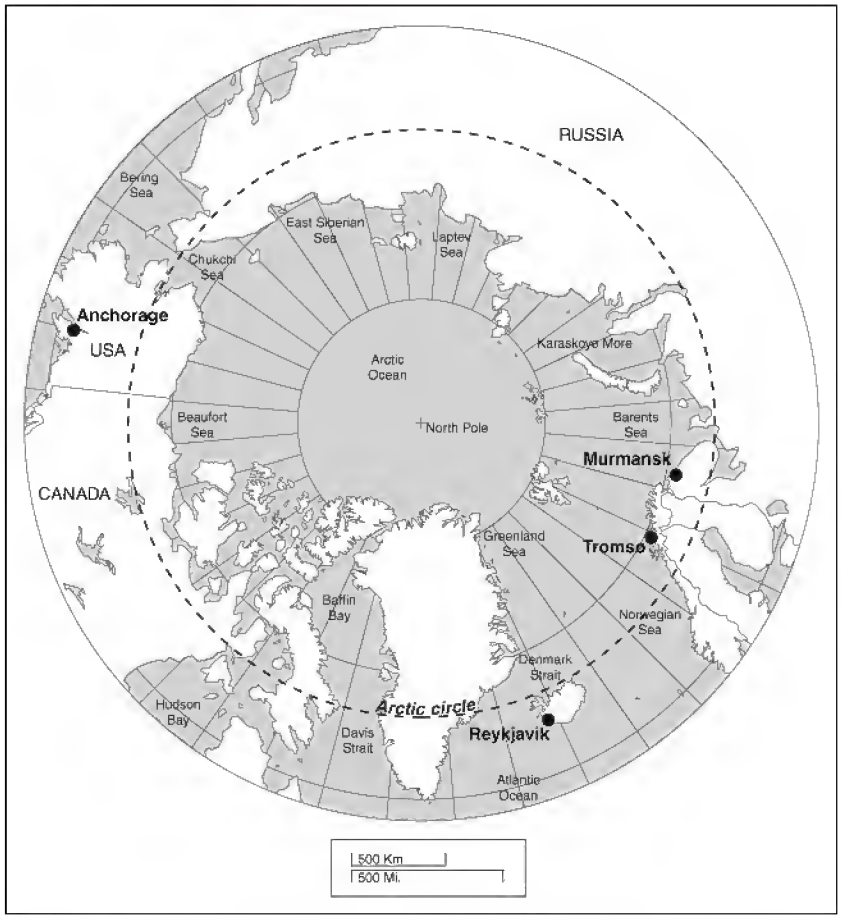

Figure 1. Map of the Arctic depicting the Arctic Circle. The neonatal intensive care unit in Tromsø is located at the same latitude as the north of Russian Siberia and the northern part of Alaska and Canada.

in the hospital, and the maternity ward was located in a separate Women's clinic, managed by nuns. In 1973, a new pediatric department, including a NICU, was built. One consultant was attached to the NICU, which was equipped rather primitively. During the following years, along with general improvements in neonatal medicine in developed countries, the NICU was further equipped and staffed. In 1991 a brand new University hospital VIDEO was opened close to the campus of the University of Tromsø. The new NICU is located adjacent to the delivery unit, which was a huge improvement compared with the previous arrangement.

Current Clinical Service

Over the past 18 years, a modern neonatal service and a NICU with advanced equipment (Table 1) and fairly generous space for patient and relatives has been created in Tromsø. Today, the NICU covers a birth population of approximately 3,000 live-born infants annually. We have the ability to care for eight intensive care (continuous positive airway pressure [CPAP] or ventilator) patients and seven intermediate patients. However, more than three to four ventilator patients are difficult to manage at one time due to limited qualified neonatal nursing staff. We deliver care to all preterm infants and sick term infants. Preterm babies routinely are resuscitated from 24 weeks of gestation; individual assessment is indicated for those born at 23 weeks. We opt for early nasal CPAP, but most of the most immature babies receive one or more periods of ventilator treatment using a volume-oriented strategy (Table 2). We practice the INSURE (INtubation SURfactant Extubation) policy for more mature babies. (4) Oral feedings with banked human milk are introduced from the first day after birth, and we try to implement developmental care early. Preterm babies who have necrotizing enterocolitis or significant patent ductus arteriosus and do not respond to medical treatment undergo surgery in the NICU. Infants who have congenital heart defects or other complex congenital malformations (eg, abdominal wall defects and diaphragmatic hernia) that require surgery in the neonatal period are transferred to the surgical centers in the south of Norway.

In 2004, a tertiary on-call system was established with four neonatologists. All neonatologists are capable of performing primary diagnosis of congenital heart defects with echocardiography. The formal on-call system ensures that around-the-clock neonatal service is available. Table 2 shows key data on outcomes of VLBW infants/infants born before 32 weeks of gestation treated in the NICU from 2003 to 2008.

Fetal medicine was established in Tromsø in 2001 and has further improved the quality of care. Improved prenatal diagnosis has many advantages for the patients, including transfer of pregnant woman to neonatal surgical centers for complex and serious malformations instead

Figure 2. The polar light (aurora borealis) seen above the city of Tromsø during wintertime. Copyright Bjørnar G. Hansen, Visit Tromsø AS. Reprinted with permission.

of complicated postnatal referrals. Neural tube defects, abdominal wall defects, and congenital diaphragmatic hernia, in particular, rarely are missed today. However, because of increased intrauterine transfer, our staff gains limited experience with these conditions. Prenatal detection of congenital heart defects is more challenging, and until recently, the detection rate was fairly low both in our region (5) and in Scandinavia in general. (6) Based on clinical studies from Norway and Sweden, (7)(8) we recently implemented pulse oximetry screening for all infants to improve early detection of critical duct-dependent heart defects.

The level of care for neonates and preterm babies is heavily dependent on the quality of nursing care. Most of our neonatal nurses have specialized education, and many have years of clinical experience in neonatal intensive care. Over the past decade, we have broadened the focus toward family-centered and individual developmental care. Our aim is to increase the competence of parents of sick and very preterm infants. Some nurses are trained in Brazelton newborn behavior assessment, and recently three nurses were fully qualified as Newborn Individualized Developmental Care and Assessment Program (NIDCAP) professionals. Using these clinical tools, we actively support and teach the parents that the behavior of the infant is its primary means of communication. (9)

Neonatal Transport

An adequate neonatal transport system is a prerequisite for equal and good service to all newborns in the Norwegian arctic region. Perhaps even more important is a constant focus on selection of risk pregnancies and intrauterine transfer, a principle also known from other parts of the world. Due to large distances, all neonatal transports in our area are conducted by air, either by fixed wing ambulance plane or by a helicopter VIDEO. The neonatal air transport team in Tromsø consists of the consultant pediatrician on call and a team of dedicated NICU nurses. Between 30 and 40 neonates are transported by this team annually. Most transports are referrals

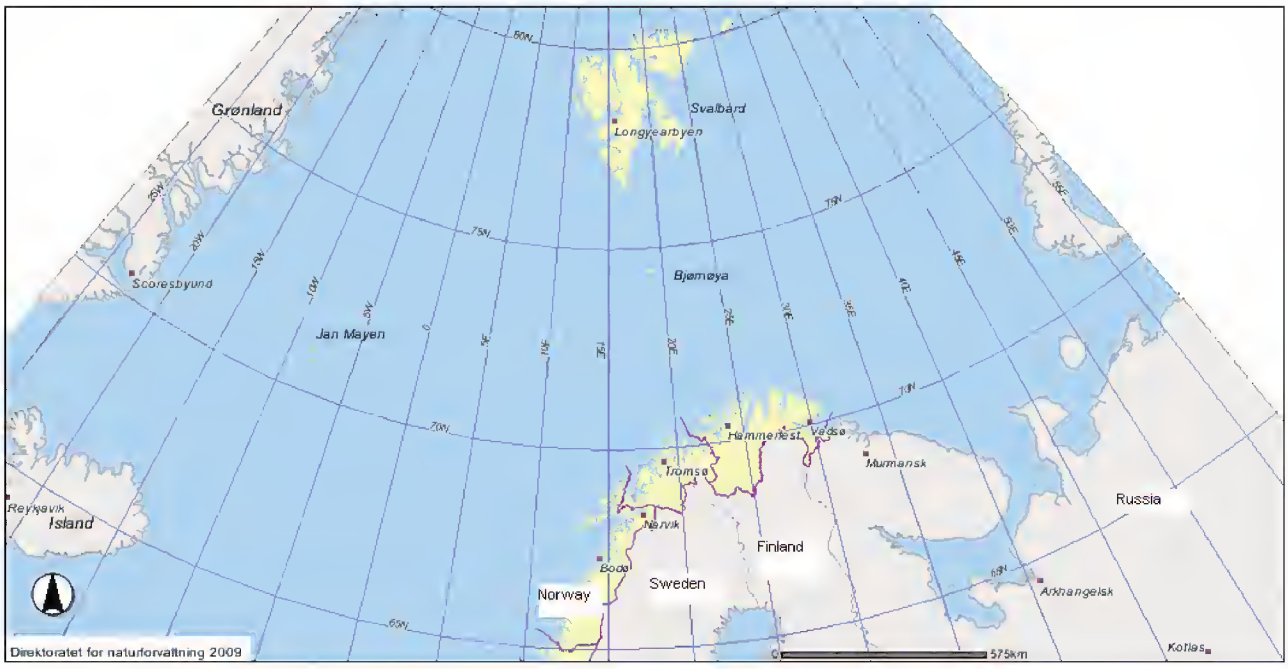

Figure 3. Geographic catchment area of the neonatal intensive care unit at the University Hospital of North Norway.

from local hospitals situated 250 to 800 km away from Tromsø. Children who have congenital heart defects requiring heart surgery during the neonatal period are transferred to Oslo University Hospital in the south of Norway, a 2½- to 3-hour flight from Tromsø. We recently published a 10-year audit of our transport activity. (10) Approximately 1% of the newborn population in our region that was born outside UNN required acute postnatal air transport to our NICU. For the VLBW population, 95% of all infants were born at UNN, the only NICU caring for this patient category. Difficult climatic conditions, with wind, snow, and poor visibility, often delays transport due to difficult takeoff and landing conditions. Therefore, training of health personnel in local hospitals and maternity homes to deal with sick neonates is important for the primary stabilization of such infants. In 2008, a modern lightweight transport incubator system replaced the previously used heavy and rather simple incubator system. The new transport incubator system facilitates patient-triggered ventilation during transport and includes an improved humidification system for patients receiving CPAP or ventilation.

Table 1. Development of New Modalities for Monitoring, Treatment, and Care in the NICU at the University Hospital of North Norway

Modality for Monitoring, Treatment, and Care	Year Introduced
Surfactant	1991
Patient triggered ventilation	1994
High-frequency ventilation	1994
Inhaled nitric oxide	1994
Brazelton newborn behavior assessment scale	1999
Continuous positive airway pressure during delivery room resuscitation of preterm infants	2001
Separate call system for neonatologists	2004
Universal otoacoustic emission screening	2007
Amplitude integrated electroencephalography monitoring	2007
Therapeutic hypothermia	2007
Pulse oximetry screening	2009
Newborn Individualized Developmental Care and Assessment Program (NIDCAP) professionals	2009

Research Focus and Activity

Clinical and basic research is an integrated part of neonatology in Tromsø. We have tried to compensate for our disadvantages relating to low patient numbers and few neo-

Table 2. **Outcome of Live Born Preterm Infants Admitted to NICU at the University Hospital of North Norway, 2003–2008**

	N	Discharged Alive N (%)	Ventilator-treated N (%)	Median Days on Ventilator (IQR)
Birthweight				
<750 g	28	14 (50)	28 (100)	17.5 (5 to 34)
750 to 999 g	50	46 (92)	39 (78)	5 (3 to 14)
1,000 to 1,499 g	89	87 (98)	22 (25)	4 (2 to 6)
1,500 to 1,999 g	143	143 (100)	10 (7)	3 (2 to 8)
Gestational Age				
23 to 25 weeks	30	15 (50)	30 (100)	26.5 (10 to 36)
26 to 27 weeks	42	39 (93)	35 (83)	5 (3 to 9)
28 to 32 weeks	173	171 (99)	33 (19)	3 (2 to 5)

IQR=inter-quartile range

natologists by creating multidisciplinary research groups and initiating collaboration with local, national, and international experts. Two focus areas for research have been outlined in relation to our NICU: a randomized, controlled trial (RCT) of a parental sensitizing intervention program in LBW infants (<2,000 g) and clinical and basic research on neonatal infections and coagulase-negative staphylococci (CoNS).

The RCT of a modified version of the Vermont Mother-Infant Transaction Program was initiated in 1999. A research group consisting of neonatologists, neonatal nurses, and neurodevelopment psychologists was formed. A cohort of LBW infants has been followed for more than 6 years, with a follow-up rate of 90%. The primary findings published to date have been positive effects in infant regulatory competence at 6 and 12 months corrected age and a sustained reduction until 24 months in parental stress reported by both fathers and mothers. The parental stress reported by the parents in the intervention group was reduced to a similar level as reported by their term peers, whereas the stress remained significantly higher among parents in the preterm control group. At 24 months corrected age, the behavioral scores were consistently better in the intervention group, but there were no differences in cognitive or motor outcome. (11)(12)(13) The outcome at 3 and 5 years follow-up will be published in the near future.

Research on neonatal infections was initiated in collaboration with microbiologists both in Tromsø and abroad. CoNS are the most frequent pathogens causing late-onset sepsis among preterm infants. (14)(15). Biofilm production is considered the major virulence factor of CoNS. (16) In a large epidemiologic study of 150 infants who had CoNS bacteremia, we found that bacteria producing biofilm caused a lower neonatal inflammatory response compared with biofilm-negative bacteria. (17) Our results supported the hypothesis that CoNS biofilm production is linked with immune evasion. Furthermore, we found that biofilm formation was associated with high levels of antibiotic resistance and the ability to persist in a NICU environment. (18) CoNS infections frequently are difficult to treat, requiring removal of central venous lines and causing high consumption of broad-spectrum antibiotics. In Norway, an aminoglycoside combined with a beta-lactam antibiotic traditionally is used for treatment of late-onset sepsis. A simplified and improved aminoglycoside dosing regimen with dosing intervals of 24 to 36 to 48 hours, based on own pharmacokinetic data, was introduced in our NICU in 2003. (19) Another study on the efficacy of different aminoglycosides revealed that arbekacin had superior antimicrobial activity against methicillin-resistant CoNS compared with traditional aminoglycosides. (20) Lately, we showed that synthetic antimicrobial peptidomimetics have higher activity on bacterial biofilms than conventional antibiotics and could be potential new therapeutic agents for biofilm-associated infections. (21)

Challenges and Limitations

Our greatest challenge as a level III neonatal service is the low numbers of sick infants due to a small patient population. The patient load in the NICU varies substantially over time. Periods with high activity are interspersed with periods of lower activity when it is difficult to maintain practical clinical training for doctors and

nurses. We also have to educate almost all neonatal nurses and future neonatologists locally. However, neonatologists in Tromsø have actively obtained clinical experience in other countries, and visiting neonatal nurses from other Scandinavian countries often bring valuable clinical and practical input from small and large NICUs.

Political debate concerning further regionalization of neonatology is ongoing in many countries. (22)(23)(24) Despite many relatively small level III units in Norway, the outcome for extremely low-birthweight infants is considered excellent. (25) However, it is challenging to maintain stable and highly competent call systems for both doctors and nurses in small units over time. Modern regulation of working hours (26) also means that a call system of at least four neonatologists is required to have an equally distributed 24-hour service. In Finland, it has been suggested that more efficient regionalization of very preterm deliveries may improve survival of such infants. (23) We also believe that a further regionalization in northern Norway would improve the care for very preterm babies.

Conclusion

Despite limitations with small patient volume, large distances between hospitals in the region, and rough climatic conditions, we believe it is possible to practice neonatology with fair results in this sparsely populated area above the Arctic Circle. It is also possible to conduct research of an international standard through collaborations with local, national, and international researchers. Norway is in the fortunate position of having a stable economy due to income from large oil and gas fields. The policy of Norwegian governments to support all areas of the country is also a prerequisite to delivery of equal health services, including high-level neonatal service, all over Norway.

ACKNOWLEDGMENTS. We thank Ganesh Acharya and Sabine Cochrane for critical reading of the manuscript.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specification

- Know the issues in the organization of perinatal care (eg, regionalization, transport quality-control, practice guidelines).

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Short Bowel Syndrome: Epidemiology, Pathophysiology, and Adaptation

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Author Disclosure
Drs Navarro, Gleason, Rhoads, and Quiros-Tejeira have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. List the primary causes of short bowel syndrome (SBS).
2. Describe regional differences in absorption by the small bowel and the role of bowel length in weaning from parenteral nutrition (PN).
3. Describe how the small bowel adapts after intestinal resection.
4. Review potential tools for assessing bowel adaptation.

Abstract

Short bowel syndrome (SBS) is a relatively common, often lethal, and highly costly medical problem in North America. Necrotizing enterocolitis (NEC) is the leading cause of SBS in the United States. An important fact to remember is that the length of the small bowel in a 28-week preterm infant is about 150 cm and in a term infant is about 250 cm. Twenty percent of this length is generally sufficient to allow dependence on parenteral nutrition (PN) via intestinal adaptation. This process is driven by significant increases in circulating trophic hormones, such as cholecystokinin, epidermal and keratinocyte growth factors, growth hormone, insulin-like growth factor-1, and glucagon-like peptide-2. These hormones produce hypertrophy and hyperplasia of the villi, along with increases in specific brush border membrane absorption mechanisms, such as glucose-sodium cotransport (via SGLT-1) and peptide transport (via Pep-T1). Currently, the best clinical markers of intestinal adaptation are the calculated percentage of enteral versus parenteral calories in a growing infant who has SBS and the serum concentrations of citrulline, an amino acid synthesized by mature enterocytes that has been used as a measure of functional intestinal mass.

Abbreviations

CCK:	cholecystokinin
CIT:	citrulline
EGF:	epidermal growth factor
GLP:	glucagon-like peptide
Hb-EGF:	heparin-binding epidermal growth factor
ICV:	ileocecal valve
IGF:	insulin-like growth factor
NEC:	necrotizing enterocolitis
NHE:	sodium/hydrogen exchanger
PN:	parenteral nutrition
PYY:	peptide YY
SBL:	small bowel length
SBS:	short bowel syndrome
SCFA:	short-chain fatty acid

Causes and Epidemiology

SBS is defined as reduced small bowel length that leads to intestinal failure. Intestinal failure is defined as inadequate intestinal absorption of nutrients, water, or electrolytes, resulting in the inability to maintain hydration and provide sufficient nutrition to support health, growth, and development. SBS usually is the consequence of extensive intestinal resection, although there are rare reports of congenital short bowel. (1) Patients who have SBS generally require unconventional nutrition support for a period of time, either PN or enteral nutrition provided as rapidly absorbed elemental formula.

SBS is a relatively common, often lethal, and highly costly medical problem in North America. Recently, a 3-year study of approximately 12,000 infants in the National Institutes of Health-funded Neonatology Research Network showed that NEC is the leading cause of SBS in the United States, with surgical short bowel syndrome developing in 1.1% of very low-birthweight infants. (2) Eight percent of infants in this

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study who developed NEC were left with SBS. Associated deficits in normal growth also were reported, and 33% continued to receive tube feedings at 18-month follow-up. A recent retrospective cohort study from Canada estimated the incidence of SBS to be 24.5 per 100,000 live births, with an associated mortality rate of 38%, even higher than that reported in the United States. (3) Mortality rates and costs in Europe are comparable to those in North America. In Graz, Austria, the overall related mortality in infants who had SBS ranged from 15% to 25%, and the annual cost per patient was $100,000 to $150,000 (United States dollars). (4)

The leading causes of SBS are neonatal NEC and congenital defects of bowel formation or rotation (Table 1).

History

The need for nutrition support of these critically ill infants led to early reports of crude attempts that sound ludicrous by modern standards. Intravenous and intraperitoneal injection of milk and other whole foods predated the demonstration by Elman and associates (5) of the use of the amino acids contained in hydrolyzed casein in 1939 and the first report of infusion of hypertonic glucose into large-caliber veins by Wilmore and Dudrick in 1968. (6)

In 1972, Wilmore published a frequently cited review of the epidemiology and prognostic factors of 50 infants who had SBS in the PN era. (7) Inclusion criteria were age younger than 2 months at operation and length of remaining small bowel of less than 75 cm of jejunoileal segment. He related the outcome to length of the residual intestine and the presence of the ileocecal valve (ICV). No infant survived with less than 15 cm of small bowel length (SBL). No infant who had ICV resection survived with less than 40 cm of SBL. All but one infant survived resection when 38 to 75 cm of SBL remained. Low birthweight and the presence of additional anomalies also were predictors of mortality, with 28 of the babies (56%) in the series weighing less than 3 kg at birth, but only 5 weighing less than 2 kg at birth and 3 of these babies dying. All of the infants had congenital gastrointestinal anomalies, with volvulus and multiple intestinal atresias being the most common and none having NEC. A more recent report showed that infants who had 15 to 38 cm of SBL have a reasonable survival and even a good chance for intestinal adaptation with or without the ICV. (8) Moreover, in the same series, the presence of the ICV had a greater impact on intestinal adaptation if the SBL was less than 15 cm.

Advances in the care and nutrition support of preterm infants have changed the epidemiology of SBS in babies. More recent reports have featured infants of much lower birthweight and much greater proportion affected by NEC (Table 2). For example, the National Institute of Child Health and Human Developmental Neonatal Research Network cites a 0.7% incidence of SBS among infants born between 2003 and 2005 whose birthweights were less than 1,500 g, 96% of whose SBS was due to NEC. (2)

Over the past 50 years, major advances have been seen in the formulation and administration of PN, such that virtually every major medical center in the United States is capable of managing a number of infants who have SBS on home PN. In addition, new surgical techniques allow the bowel to be lengthened. Finally, small bowel transplantation is now not a rare procedure, and improvements have been made in immunosuppression, leading to increased duration of survival.

Table 1. Intestinal Diseases and Anomalies Associated With Short Bowel Syndrome in Infants

Necrotizing enterocolitis
Intestinal atresia
• Jejunal • Ileal • Multiple (Christmas tree/apple peel deformity)
Midgut volvulus
• Malrotation • Adhesive bands
Abdominal wall defects
• Gastroschisis • Omphalocele
Meconium ileus
Thrombotic disorders
• Inherited • Sepsis-related
Trauma (eg, swimming pool accidents, nonaccidental trauma)
Hirschsprung disease involving the small bowel
Congenital short bowel syndrome

Table 2. **Changing Pattern of Causes and Mortality of Short Bowel Syndrome**

Date of Report	Number Having Intestinal Anomalies (%)	Number Having Necrotizing Enterocolitis (%)	Mortality Rate (%)	Reference
1972	50/50 (100)	0	16/50 (32)	Wilmore (7)
1986	(71)	(29)	—	Ziegler (9)
1998	19/34 (56)	15/34 (44)	4/34 (12)	Sondheimer (10)
2001	17/30 (57)	13/30 (43)	9/30 (30)	Andorsky (11)
2004	62/78 (80)	16/78 (20)	21/78 (27)	Quiros-Tejeira (12)
2008	11/19 (56)	8/19 (44)	2/19 (11)	Salvia (13)
2008	4/89 (4)	85/89 (96)	(50)	Cole (2)

Pathophysiology and Adaptation

Depending on the extent and location of the intestinal resection, patients who have SBS lose site-specific transport systems that affect nutrient absorption and water and electrolyte balance in the intestine. For clinical practice purposes, intestinal adaptation is defined as the ability to maintain normal growth and fluid and electrolyte balance without the need for PN. (8)

Regional Differences in Absorption

Physiologically, the duodenum and proximal jejunum absorb sodium and water, fat-soluble vitamins, and minerals such as calcium, magnesium, phosphorus, and iron. These solutes should be monitored after resections of the upper intestine. In this portion of the intestine, mixing of bile and pancreatic secretions allows micellar solubilization and intraluminal digestion; its absence may affect normal digestion.

Movement of water and electrolytes (ie, secretion) from the plasma to the lumen occurs in the upper jejunum. Patients who have undergone jejunostomy may develop "end-jejunostomy syndrome," which is characterized by hyponatremia, hypokalemia, hypomagnesemia, and dehydration.

In the ileum, sodium chloride is absorbed actively, accompanied by passive influx of water. (14)(15) Bile salts and vitamin B12 are absorbed by active transport mechanisms in the terminal ileum. Therefore, resection at this level may lead to vitamin B12 deficiency, steatorrhea (due to bile salt loss), and diarrhea (due to malabsorbed bile salts that increase the secretion of water and electrolytes in the colon). (16)

The colon has the capacity to absorb water and electrolytes. The colonic mucosa also can absorb nutrients; the colon "salvages nutrients" by absorbing short-chain fatty acids (SCFAs). The SCFAs come from degradation of malabsorbed carbohydrates and proteins by bacterial enzymes. SCFAs are absorbed by a mechanism involving their exchange for bicarbonate. (17) It has been estimated that this process can generate up to 1,000 kcal/day in energy supply. (18)

The degree of malabsorption in SBS depends on the location and extent of resection as well as the preservation of the ICV. The ICV, which regulates the exit of fluid and nutrients from the ileum into the colon, also is called the "ileal break." The break mechanism is especially important after extensive intestinal resections. The ICV also prevents the reflux of colonic bacteria into the small bowel, protecting against small bowel bacterial overgrowth. (19)

Small Intestinal Length

The length of residual intestine is the most important factor to determine dependency on PN. Term babies are born with 250 to 275 cm of small bowel. Necropsy series have shown that at 25 weeks' gestation, infants have approximately 100 cm of total small bowel (20) and approximately 200 cm of small bowel at 30 weeks' gestation. (21) The normal length of small bowel in adults has been reported to be as long as 850 cm. Patients who have less than 30% of normal small bowel length are at risk of developing SBS. A study of infants who had SBS showed that the theoretical chance of weaning from PN is less than 50% if the remaining intestine is less than 30 cm, 60% if it is 60 cm, and almost 100% if it is 100 cm. (11) However, in a 25-year follow-up study from one center, investigators demonstrated more than 80% survival after weaning from PN in all infants who had more than 15 cm residual small bowel. For infants who had less than 15 cm small bowel remaining, the survival was 38%, including three of four who had intact ICVs. (12) None of the four infants who did not have ICVs and who had less than 15 cm small bowel survived. It is unclear if such remarkable results can be applied to all tertiary referral centers.

Intestinal continuity also is an important factor that has a significant impact not only on survival but in the intestinal adaptation process. (8) Another factor that enhances the potential for intestinal adaptation in children is the increase of small bowel length accompanying

normal growth, which is significant from birth through ages 3 to 4 years. (22)

Small Bowel Adaptation

The initial malabsorption after intestinal resection in SBS improves due to adaptive changes in the remaining intestinal mucosa, occurring as early as 48 hours postoperatively (Fig. 1). Both structural and functional changes are observed. The structural adaptation includes hypertrophy and hyperplasia, with an increase in the height and diameter of intestinal villi, thereby increasing the absorptive area. (23) Interestingly, apoptosis of enterocytes migrating up the villi does not decrease during villus hyperplasia, as might be expected. In fact, there is a marked increase in apoptosis in SBS, which can be reduced by peptides such as epidermal growth factor (EGF). (24) Over time, intestinal dilatation may occur, lengthening and thickening the bowel. The functional component of adaptation encompasses changes in nutrient transport, enzymatic activity, and intestinal transit. This adaptive process could take up to 2 years and may determine if a patient can escape intestinal failure and dependency on PN. (25)

Because luminal nutrients are important for small bowel adaptation, enteral nutrition should start early. Intestinal hyperplasia is the result of increased crypt cell proliferation mediated by several growth factors, which are released in the presence of food and biliary and pancreatic secretions in the intestinal lumen. (8)(26)(27)(28)(29) Nutrients also provide substrate for the proliferation of enterocytes. Glutamine, SCFAs, unsaturated fat, ornithine, and nucleotides are among the nutrients that have been cited as trophic. (30)(31)(32) Glutamine is the primary substrate used by enterocytes and is important for the synthesis of nucleic acids. In addition, glutamine is a primitive growth factor for intestinal cells that signals via mitogen-activated protein kinases. (33)

Animal models of SBS have documented both translational and posttranslational changes (in the process of adaptation) that make absorption of nutrients more efficient (Fig. 2). For example, absorption by the sodium-glucose cotransport system (SGLT-1) has been reported to increase. (34) Investigations in a rabbit model showed a twofold increase in glucose-sodium cotransport, (35) which includes the de novo appearance of two sodium-dependent glucose transporters in the ileum following bowel resection. (36) Another example of increased absorptive function is the appearance of the oligopeptide Pep-T1 transporter, which appears de novo in the colon only after small bowel resection, providing a mechanism for salvage of malabsorbed amino acids. (37)(38) During the interdigestive period, when no amino acids or glucose are available to be coupled to sodium transport, absorption occurs via coupled sodium/hydrogen and chloride/bicarbonate exchangers. In experimental SBS, electroneutral sodium absorption via sodium/hydrogen exchanger-3 (NHE-3) is increased. (39) In addition, several aquaporin (water channel) mRNAs were found to increase in rat ileum and colon after bowel resection. (40)

Important Role of Systemic and Local Growth Factors

Enteric hormones contribute to the adaptation process of SBS, as shown in animal studies. Hormones proposed to mediate these effects include enteroglucagon, cholecystokinin (CCK), gastrin, EGF, heparin-binding EGF (Hb-EGF), keratinocyte growth factor, neurotensin, leptin, growth hormone, insulin-like growth factors (IGF)-1 and -2, peptide YY (PYY), neurotensin, and insulin. (28)(29)(32)(41) Thus, many cells orchestrate a complex adaptive response, including enteroendocrine cells (enteroglucagon), L-cells of the ileum (glucagon-like peptide-2 [GLP-2]), the submandibular and Brunner's glands (EGF), intestinal smooth muscle cells (Hb-EGF), the liver and small intestine (IGFs), gastric G-cells (gastrin), duodenal enteroendocrine cells (CCK), enteric neurons (PYY and neurotensin), and pancreatic beta cells (insulin). The release of most of these hormones is induced by luminal nutrients. The exact role of these hormones in human SBS has not been established, but they may affect polyamine metabolism. Polyamines are synthesized in large amounts from ornithine by rapidly proliferating tissues such as the intestine undergoing adaptation and have been implicated in the regulation of intestinal adaptation. Polyamines are rapidly obtained from a diet supplemented by ornithine alpha-ketoglutarate, an arginine and glutamine precursor, which has been shown to improve intestinal adaptation in animal models. (34)

GLP-2, an antisecretory hormone that regulates intestinal transit, currently is considered one of the most important gastrointestinal hormones in intestinal adaptation. (42)(43) It is secreted by the L cells in the terminal ileum and colon in response to nutrients. GLP-2 increases intestinal blood flow, and it reverses villus atrophy seen in PN-fed newborn piglets. (44) In patients who have SBS and a remaining colon, GLP-2 is elevated. (45) GLP-1 and -2 concentrations are increased in patients who have undergone intestinal resection in whom the colon has been preserved. In animal models involving colon removal, GLP-2 supplementa-

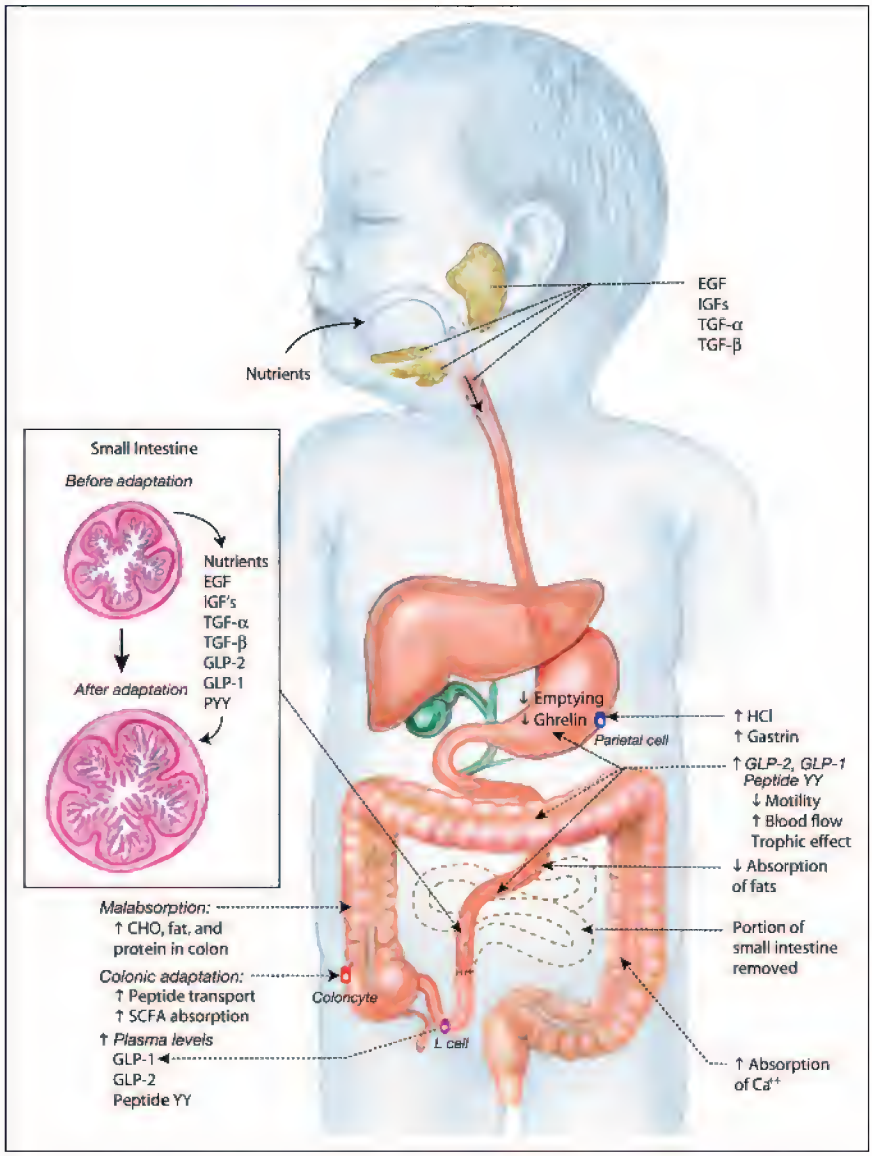

Figure 1. Adaptive response of the gastrointestinal tract to small bowel resection. Salivary hormones and nutrients provide luminal growth factors, while intestinal cells, especially the ileal L-cell, produce growth factors such as enteroglucagon, which is cleaved into the active components GLP-2 and GLP-1. These cells also produce peptide YY (PYY). The three hormones produce effects such as increased intestinal blood flow, decreased gastric emptying and small bowel motility, and trophic effects on the mucosa. Reduced ghrelin in response to peptide YY causes a reduced appetite. Malabsorption of protein may lead to increased peptide transport in the colon and malabsorption of carbohydrate leads to increased short-chain fatty acid (SCFA) concentration in the colon, which is trophic and leads to increased capture of malabsorbed calories. Increased gastric acid secretion may be transient, but has led in experimental animals to ulcer formation shortly after bowel resection. The inset at the left lists many of the major growth factors and shows adaptational changes at the epithelial level, which include taller villi and an increased bowel luminal diameter. Increased calcium and oxalate absorption from the colon can predispose to nephrocalcinosis. CHO=carbohydrate, EGF=epidermal growth factor, GLP=glucagon-like peptide, IGF=insulin-like growth factor, TGF=transforming growth factor. Illustration by Barbara Siede, Ochsner Clinic Foundation, New Orleans, La.

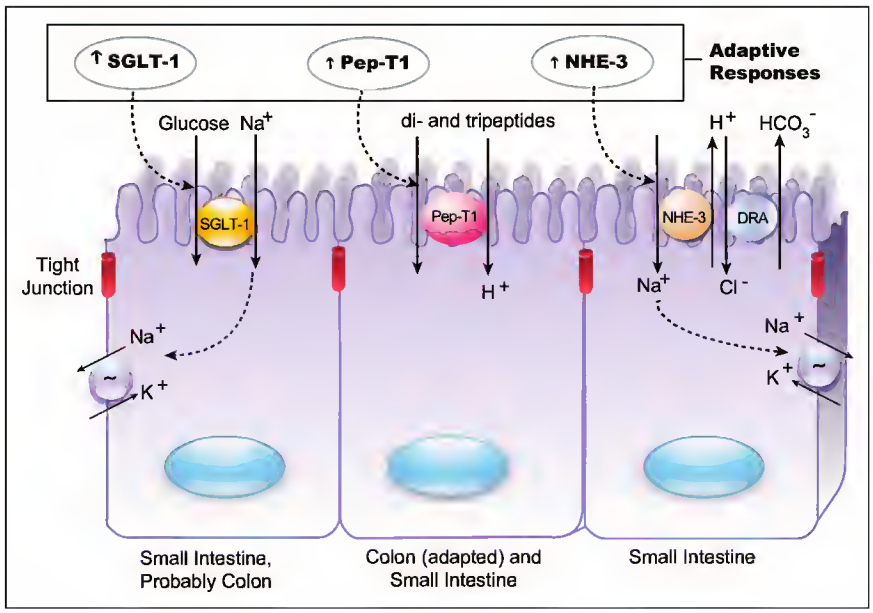

Figure 2. Adaptive changes in epithelial cellular transport mechanisms. These include increased glucose-sodium transport via SGLT-1 in the small intestine (and probably large intestine); increased peptide (di- and tripeptide) absorption in the colon and small intestine; and increased neutral sodium chloride absorption in the small intestine via the coupled brush border sodium/hydrogen (NHE-3) and chloride/bicarbonate exchangers (DRA). Such changes result in increased retention of sodium, glucose, and peptides. Illustration by Barbara Siede, Ochsner Clinic Foundation, New Orleans, La.

tion has induced villous hyperplasia. In humans who have SBS, ileocolonic resection affects the production of GLP-2. It has been reported that GLP-2 therapy increases the intestinal villus length/crypt depth ratio, while enhancing weight gain, absorption of protein, and body mass accretion. Its clinical use is under investigation. (46)(47)

Negative regulation of adaptation also can occur. In a rat model, investigators compared bowel adaptation following 70% bowel resection in the presence or absence of endotoxemia. (48) Endotoxin treatment reduced mucosal weight, DNA content, and villus height, especially in the ileum.

Gastrointestinal motility also may be affected in patients who have SBS due to abnormal concentrations of enteric hormones. For example, faster gastric emptying and rapid small bowel transit are found in patients who have jejunostomy or ileal resection. PYY as well as other hormones such as GLP-1, GLP-2, and neurotensin are produced in the terminal ileum and colon and are released in the presence of luminal nutrients such as fat and carbohydrates. These hormones slow gastric emptying and gastrointestinal transit. When these hormones are decreased, the slowing effect of fat on gastrointestinal motility is impaired. (30)(49)

Knowledge of the effect and roles of nutrition and hormones (eg, growth hormone) in SBS has generated new therapeutic approaches. (43)(50) Reports on both animal models and in humans indicate that administration of the combination of growth hormone and glutamine allows a significant reduction in PN requirements. (51) The benefits of exogenous glutamine in intestinal adaptation have not been demonstrated in trials by other investigators. (52)(53) No placebo-controlled trials of glutamine and growth hormone in infants or children who have SBS have been published.

Potential Tools for Assessing Adaptation

Measuring the degree of enteral tolerance is used to assess small bowel function. A study in infants showed that the percentage of feedings that were tolerated enterally at *3 months after intestinal resection* could predict PN weaning. (10) Infants who had 25 cm of residual small bowel and were able to tolerate 75% of calories enterally had a 90% chance of weaning from PN. On the other hand, those able to tolerate 25% or less of calories enterally had a 50% chance of weaning from PN.

Citrulline (CIT) is a nonprotein amino acid almost exclusively produced by enterocytes that is present in minimal amounts in the diet. Studies have shown plasma CIT concentrations to be reduced in patients who have SBS. Plasma concentrations of CIT change over time, as intestinal adaptation occurs. CIT progression could distinguish between patients who have transient and permanent intestinal failure. (54) In children who have SBS, plasma CIT values can estimate the amount of enteral calories that patients can tolerate without developing diarrhea. (55) In addition, this study and studies in adults showed that plasma CIT closely correlates with the residual small bowel length. CIT has been proposed as a marker of enterocyte mass and short bowel function as well as a predictive factor for weaning from PN. (56) Sequential measurement of CIT may allow assessment of whether bowel adaptation is progressing.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specification

- Know the clinical features, complications, and management of short gut syndrome.

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NeoReviews Quiz

1. The incidence of SBS, based on a retrospective cohort study from Canada, is estimated at 24.5 per 100,000 live births. Of the following, the *leading* cause of SBS is:

   A. Gastroschisis.
   B. Hirschsprung disease.
   C. Inherited thrombotic disorder.
   D. Meconium ileus.
   E. Necrotizing enterocolitis.

2. The length of the residual jejunoileal segment and the status of the ileocecal valve determine the potential for survival in infants who have SBS. Of the following, the critical length of jejunoileal segment necessary for survival in the absence of the ileocecal valve, based on an epidemiologic study by Quiros-Tejeira and associates, is:

   A. 15 cm.
   B. 40 cm.
   C. 65 cm.
   D. 90 cm.
   E. 115 cm.

3. Nutrient absorption within the gastrointestinal tract differs according to region. Of the following, the site of maximal absorption for vitamin B12 is the:

   A. Ascending colon.
   B. Duodenum.
   C. Ileum.
   D. Jejunum.
   E. Stomach.

4. Intestinal adaptation in SBS encompasses a structural component of changes in intestinal villi that increase the absorptive surface area of the gut as well as a functional component of changes in nutrient transport, enzymatic activity, and intestinal transit. Of the following, the hormone *most* important for regulation of intestinal transit in the process of intestinal adaptation is:

   A. Cholecystokinin.
   B. Gastrin.
   C. Glucagon-like peptide-2.
   D. Peptide YY.
   E. Leptin.

5. Luminal nutrients, provided through enteral nutrition, are important for intestinal adaptation in SBS. Of the following, the primary substrate used by enterocytes in the process of intestinal adaptation, which increases intestinal cell proliferation via mitogen-active protein kinases, is:

   A. Glutamine.
   B. Nucleotides.
   C. Ornithine.
   D. Short-chain fatty acids.
   E. Unsaturated fat.

6. Several clinical markers of intestinal adaptation have been studied for prognostication in infants who have SBS. Of the following, the best serum marker reflective of enterocyte maturation in intestinal adaptation is the amino acid:

   A. Arginine.
   B. Citrulline.
   C. Glutamine.
   D. Histidine.
   E. Ornithine.

Short Bowel Syndrome: Complications, Treatment, and Remaining Questions

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Author Disclosure
Drs Navarro, Gleason, Rhoads, and Quiros-Tejeira have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives

After completing this article, readers should be able to:

1. Describe the common complications associated with short bowel syndrome (SBS).
2. Describe treatments for SBS.
3. Discuss appropriate monitoring of patients who have SBS.
4. Review the status of small bowel lengthening procedures and transplantation for SBS.

Abstract

This review deals with the complications and treatment of short bowel syndrome (SBS), addressing the psychosocial, medical, and surgical complications in children receiving long-term parenteral nutrition (PN) support, as well as factors that affect the intestinal adaptation process. Whenever possible, as much of the colon as possible is retained in continuity because the colon is an avid absorber of sodium. It is also important for clinicians to be aware of the important absorption mechanisms in the different regions of the bowel. For example, resection of the terminal ileum removes vitamin B12 transporters and active sodium-coupled bile salt transporters. Treatment of patients missing the terminal ileum may require monthly vitamin B12 injections and oral bile salt binders, such as cholestyramine, when the colon is present to reduce the volume of diarrhea. Patients who do not have ileocecal valves (ICVs) are prone to small bowel bacterial overgrowth that requires treatment to facilitate the intestinal adaptation process. We discuss how the PN is decreased as enteral feedings are advanced as well as clinical monitoring and routine laboratory tests. Although much has been learned over the past 20 years about PN, major questions remain, including determining the optimal form of intravenous lipid (omega-3 preparations versus omega-6 lipids versus a combination of both) to prevent liver disease.

Abbreviations

GH:	growth hormone
GLN:	glutamine
HCLF:	high-carbohydrate/low-fat
ICV:	ileocecal valve
LCT:	long-chain triglyceride
LMWH:	low-molecular weight heparin
MAPK:	mitogen-activated protein kinase
MCT:	medium-chair triglyceride
NEC:	necrotizing enterocolitis
PN:	parenteral nutrition
SBBO:	small bowel bacterial overgrowth
SBS:	short bowel syndrome
STEP:	serial transverse enteroplasty procedure
UDCA:	ursodeoxycholic acid

Complications of SBS

Psychosocial

The physician's perception has been that children receiving PN have miserable lives, with recurrent infections and a high mortality rate. These events are not uncommon, particularly in the first year after birth. However, both European and North American outcome data document that younger patients receiving home PN have better survival than older patients, approaching 90% at 1 year. (1) Recently, a French multicenter questionnaire study showed that the quality of life of children dependent on home PN and their siblings was not different from that of healthy children, suggesting the use of effective coping strategies. In contrast, the quality of life of parents of children dependent on home PN is low and is associated with high rates of depression.

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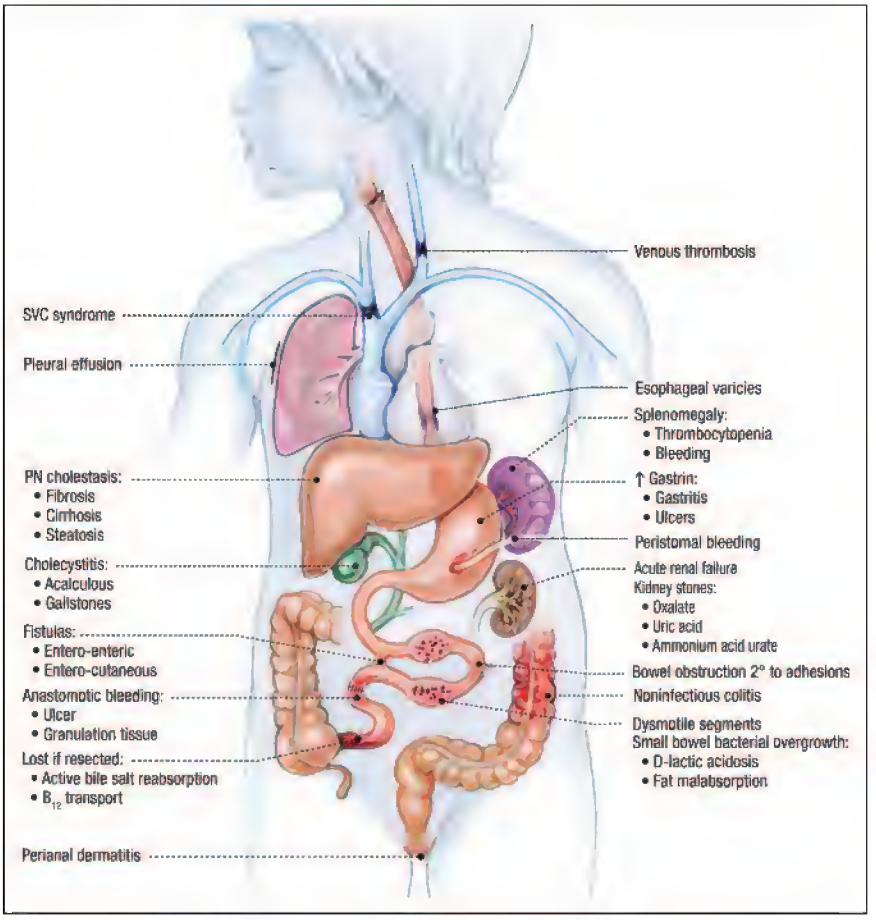

Figure 1. The most frequent and severe complications of short bowel syndrome and chronic parenteral nutrition (PN) in infants and children. SVC=superior vena cava. Illustration by Barbara Siede, Ochsner Clinic Foundation, New Orleans, La.

Medical

Medical complications and mechanisms of bowel adaptation are summarized in Figure 1. Chronic liver disease due to PN-associated cholestasis has supplanted sepsis, dehydration, and malnutrition as the most common cause of death in infants who have SBS.

SEPTICEMIA. Central line infections are common in both infants who are hospitalized and those receiving home PN. The infection rate is much higher in children than in adults. (2) The number of infections in infants gradually declines with increasing postnatal age. Unexpectedly, the number of infections is much lower in infants who are cared for by their biologic mothers in their own homes. (3) There are many reasons why these babies are prone to septicemia. Even healthy babies are covered with a "fecal veneer" of gram-negative organisms, and those who have SBS have more stools and more enteric microflora on the skin. Older infants and toddlers touch, bite, and pick at their central lines, breaking down the integrity of the intravenous access device.

In the literature, the three most important infectious agents associated with septicemia (in order of frequency) are gram-positive cocci, especially coagulase-negative staphylococci; gram-negative rods; and fungi, especially *Candida albicans*. (4)(5) However, in our experience, infections with enteric organisms greatly outnumber infections with skin organism (eg, staphylococci, *Candida*) (Table). During a 1-year period, babies who had SBS and were receiving PN developed 23 central line infections with enteric organisms compared with 14 infections with skin organisms. Of note, 19 infections were associated with a single organism, but 10 infections were associated with at least two organisms.

Gram-positive and fungal infections presumably are related to poor skin care and possibly to skin entry across regions of skin breakdown, include gastrostomy and ostomy sites and sites of perianal skin excoriation. However, gram-negative organisms could enter the bloodstream via skin sites or via bacterial translocation across the gut. Indeed, SBS in animal models is associated with increased bacterial translocation to the mesenteric lymph nodes and liver. The mechanism, although not clearly defined, is not associated with an increase in intestinal paracellular permeability. (6) The increase may relate to greater bacterial movement directly across the enterocyte into the lamina propria or entry across an ulcerated surface epithelium. Protection by phagocytic Kupffer cells in the liver sinusoids may be more essential than mesenteric lymph node clearance, based on increased bacterial dissemination to liver, spleen, and lungs when Kupffer cells are inactivated by gadolinium treatment. (7) Recently, the mechanism of translocation of endoluminal nonpathogenic *Escherichia coli* was studied in intestinal cell monolayers. The investigators found that "focal leaks" in the epithelium were associated with bacterial elaboration

Table. **Infectious Organisms Isolated Central Line Blood Cultures***

- *Bacillus* sp
- *B cereus*
- *Candida lusitaniae*
- *C nanalbicans*
- *C parapsilosis (3)*
- *C tropicalis*
- *Citrobacter farmeri*
- *C koseri*
- *Escherichia coli (2)*
- *Enterobacter cloacae (2)*
- *Enterococcus (6)*
- *Klebsiella oxytoca (2)*
- *K pneumoniae (4)*
- *Lactococcus*
- *Pseudomonas aeruginosa (2)*
- *Serratia marcescens*
- *Staphylococcus aureus (3)*
- *S "nonaureus" (6)*

*Data from babies who have short bowel syndrome and parenteral nutrition-associated sepsis at University of Texas at Houston in 2008. Numbers of discrete infections are shown in parentheses. n=19 single-organism infections. n=10 mixed infections (≥2 organisms).

of an alpha-hemolysin, as if the bacteria were "drilling into the mucosa." Translocation was markedly enhanced by exogenous interleukin-13 and tumor necrosis factor-alpha. (8)

Breaks or fractures of the central line can occur, and sepsis is an almost inevitable consequence. Measures aimed at reducing "fidgeting with the line" often are helpful. These include wrapping the infant in a cloth mesh or covering with a tight "onesie" shirt so the line cannot be pulled. On occasion, parental negligence is suspected, and there may be value to the difficult consideration of changing caretakers, which can produce life-saving results.

CHOLESTASIS. During the 1970s and 1980s, as PN was developing into a viable treatment for preterm infants, physicians noted that cholestatic liver disease occurred within 2 to 4 weeks of PN commencement, manifested by a "transaminitis." (9) PN cholestasis occurred the earliest in SBS patients who had three risk factors: prematurity, nothing by mouth status, and septicemia. However, additional factors associated with motility disturbance and poor gut integrity were believed to be important. As to which component of the PN is "the injurious factor," research has identified each macronutrient component of the PN (amino acids, soybean oil, and glucose) as a contributing factor. (9)(10) Phytosterols, which are present in the soybean emulsion and at high concentrations in the serum of individuals receiving PN, have been found to create a fatty liver in experimental animals. (11)(12) Progression of the cholestasis also is related to endotoxemia, which is more likely in infants who have SBS and is associated with motility problems, leading to bacterial overgrowth of the small bowel. (13)(14)(15)

Physicians have long tried to identify the "smoking gun" in PN that injures the liver in neonates. Studies that implicated amino acids found that cysteine (an important component of the major liver antioxidant glutathione) was low. A preparation designed to normalize serum amino acid concentrations that contained increased cysteine and supplemental taurine was developed for preterm infants. Subsequently, a meta-analysis showed that within specific subgroups of neonatal patients, taurine supplementation protected against PN-associated cholestasis. (16) A relatively large controlled trial in very low-birthweight infants and postsurgical infants supported this conclusion. Conversely, PN containing the standard amino acids was associated with a twofold increase in the incidence of PN-associated cholestasis compared with periods of exclusive feeding with the taurine-supplemented PN formulation. (17)

Although PN-associated cholestasis normally develops before heavy metal accumulation in the liver, cholestasis is associated with accumulation of iron, copper, and chromium, each of which can perpetuate a vicious cycle. Hepatic accumulation of iron from the PN may injure the liver, and serum iron values should be monitored. (18) Copper accumulation in the range of concentrations seen early in Wilson disease is not unusual in PN-dependent patients, but copper overload seems independent of duration of PN and may be a sign rather than a cause of liver disease. (19) Reduction or removal of copper from the trace elements added to PN sometimes is indicated in a child who has cholestasis. However, we have seen hypocupremia resulting in neutropenia occurring within months after removal of copper from the PN.

An interesting observation has been that the cholestasis set in motion by PN in children who have SBS does not resolve rapidly after PN is discontinued. In a recent study from Singapore designed to determine the duration of PN-associated cholestasis in preterm infants, ursodiol was administered to postsurgical infants after PN had been stopped. (20) The dose was 15 to 20 mg/kg per day in two divided doses. Ursodiol was continued

until liver function normalized. Compared with previous therapy, ursodiol significantly reduced serum bilirubin and aspartate aminotransferase concentrations, but a mean duration of 4 months was required for full normalization of liver function. The serum alanine aminotransferase was the last marker to respond, at a mean duration of 3.8±0.8 weeks. We also have observed that children who have SBS in whom PN has been discontinued and who are not fully tolerant of enteral feeding may experience a worsening of cholestasis until nutrition status can be improved.

THROMBOSIS. The survival of an infant who has SBS is contingent on maintaining the patency of his or her central veins. However, thrombosis of the primary veins that are used for catheter sites (internal jugular, subclavian, and saphenous) after months of PN is almost universal. Thrombosis occurred in about 7% of 510 infants in one study; (21) if related to the superior vena cava, the thromboses led to complications such as head and neck swelling, as well as pleural effusions. The authors suggested that catheters in the inferior vena cava were less likely to produce symptoms. However, others have preferred to avoid saphenous veins because of their greater likelihood to become infected with fecal organisms from the diaper area.

Venous thromboses are believed to be related to infection because infection often is noted when the line becomes thrombosed. When lines are removed, the veins usually "clot off." However, some catheters become obstructed spontaneously. Thrombosis is more likely with increasing tonicity of the PN, and most physicians are careful to provide dextrose concentrations no greater than 17%. Lipid infusion in the catheter may reduce the thrombosis risk. (22) However, hypercoagulable states are not rare, and screening for conditions such as protein S and C deficiency, antithrombin deficiencies, and the factor V Leiden mutation may be helpful.

With increasing duration of PN, significant problems with venous obstruction are seen. Superior vena cava syndrome is common and can lead to macrocephaly. (23) To reduce the risk of thrombosis, administration of anticoagulants has been advocated. (24) Our practice has been to administer low-molecular weight heparin (LMWH) subcutaneously to any infant who has SBS, has developed thromboses in two primary central line sites, and is expected to require PN for an extended period of time. LMWH offers many advantages over unfractionated heparin due to the longer half-life, increased bioavailability, ease of administration, and ease of monitoring in children. However, a Cochrane review of 10 eligible studies in which heparin was administered either as a flush solution or as an additive to the PN solution did not show a benefit of anticoagulation. (25) The results could not be combined for meta-analysis due to significant heterogeneity of the treatment effect, but there were no significant differences between the heparin and the placebo/no treatment groups with respect to the risks of infiltration, phlebitis, or intracranial hemorrhage. To our knowledge, no randomized, controlled trials of LMWH have been performed in patients who have SBS and are receiving PN.

SMALL BOWEL BACTERIAL OVERGROWTH (SBBO). SBBO (also called "blind loop syndrome") is defined as the presence of at least 10^5 bacteria/mL of proximal small bowel aspirate. About 60% of children who have SBS develop SBBO, and those who develop this complication are less likely to wean off PN. Predisposing factors include proximity of the colonic flora to the proximal intestine and reduced bowel motility. Although the lack of an ICV traditionally has been presumed to be associated with SBBO, an absent ICV was not found to be a risk factor in a large series from Omaha (15) or in a small series from Milan. (26) In the Omaha series, reduced length of small bowel was a significant risk factor. (15) The organisms identified in bacterial overgrowth are often anaerobes or gram-negative bacteria. As a consequence of microbial proliferation within the duodenojejunum, intraluminal bile salts are deconjugated, resulting in failure of micellar solubilization and steatorrhea. In addition, these organisms produce enzymes such as elastase that are known to reduce the activities of brush border digestive enzymes, such as lactase. (27) Another consequence of bacterial overgrowth is the systemic absorption of endotoxin, which contributes to autoinflammatory diseases such as bile duct inflammation (cholangitis) and reactive arthritis. (28) Strong experimental evidence supports the widespread clinical opinion that increased bacterial cell wall products, such as peptidoglycan and lipopolysaccharide, underlie the pathophysiology of PN-associated liver disease. (29)

Although the efficacy of prophylaxis against bacterial overgrowth in SBS has been debated, evidence for its presence is strong. Recently, one group studied the efficacy of endoscopic procedures for children who have SBS (n=27). (30) Seventy percent of procedures demonstrated abnormalities, which included gross endoscopic abnormalities, abnormal biopsies, and positive cultures. The authors demonstrated infection in 20%, anatomic abnormalities in 18%, ulcerations in 15%, and allergic disease in 15% of patients. SBBO was proven in

11 (73%) of 15 duodenal cultures. It was not stated if *Clostridium difficile* colitis was identified, but in our experience, colitis with pseudomembranes is rarely, if ever, seen, even when the toxin of *C difficile* is identified in the stool.

GALLSTONES. The composition of bile is altered toward a bile salt-depleted, lithogenic form of bile in patients who have ileal resection, and up to 25% of infants who have SBS develop cholelithiasis. In adults, PN-associated gallstones are associated with cholecystitis and pancreatitis, and prompt surgery is recommended. (31) Infants receiving chronic PN should not receive the antibiotic ceftriaxone because it has been reported to crystallize and produce pseudolithiasis in children. (32) One pediatric study indicated that gallbladder emptying is more efficient with bolus feeding than with continuous feedings. Because the latter is employed most often in those who have SBS to maximize absorption, there is debate about the optimal approach to feeding such infants. (33)

A treatment that we and others routinely administer to infants who have SBS-associated PN cholestasis is oral ursodeoxycholic acid (UDCA) because of its efficacy in other cholestatic conditions. Recently, a trial investigating very low-birthweight infants from Taipei showed that patients who received UDCA therapy at doses of 10 to 30 mg/kg per day had shorter durations of cholestasis than the control group (63 versus 92 days, $P=0.006$). (34) Furthermore, the peak serum value of direct bilirubin was significantly lower in the UDCA group.

D-LACTIC ACIDOSIS. D-lactate is produced by lactobacilli, *Bacteroides,* and other gram-positive bacteria in the intestine. It is normally absent in human serum, but in children who have SBS, the D-lactate concentration averages around 500 mcM (35) and can exceed a concentration of 141 mM. It is not unusual for an infant who has SBS to present with hyperchloremic metabolic acidosis, encephalopathy, and hypotension. In this setting, overfeeding and septicemia are the first conditions suspected. However, it is essential to recognize that these findings may be caused by D-lactic acidosis. D-lactic acidosis can be recurrent and can be lethal. D-lactic acidosis usually is treated by stopping oral intake of carbohydrates and enterally administering an antibiotic directed at gram-positive pathogens (eg, vancomycin). (36) D-lactic acidosis probably is the end result of a number of aberrations, including increased small bowel malabsorption, abnormal colonic flora, reduced colonic motility, and decreased lactate metabolism. It is an interesting and often forgotten observation that lactobacilli and *Bacteroides* may constitute more than 60% of the fecal organisms in children who have SBS. (37)

GASTROINTESTINAL BLEEDING. Increased gastric acid secretion and hypergastrinemia is a common but not universal finding during the immediate months following significant (>66%) bowel resection. (38) Ulcers in the upper digestive tract can be seen during this period, and acid blockers generally are administered after bowel resection in infants expected to require prolonged PN. Hypergastrinemia resulting from gastric antral G-cell hypersecretion, combined with decreased small bowel gastrin degradation, may be the mechanism. Gastric and duodenal ulcers associated with short gut are managed by acid blockers. (39) However, after years of PN, upper gastrointestinal bleeding more often is related to portal hypertension and includes bleeding from gastrostomy tube sites and variceal bleeding.

Babies who have SBS often develop blood-streaked stools. Associated causes include perianal dermatitis with excoriation, granulation tissue at internal anastomotic sites, (40) and noninfectious colitis. Occult or overt gastrointestinal bleeding can be associated with bowel-bowel anastomoses, and our experience agrees with that of the group in Toronto that this type of bleeding may be related to local ischemia, can be severe enough to require multiple transfusions, and generally responds only to surgical revision of the anastomotic site. (40)

Noninfectious colitis is probably less common in the current era of amino acid formulas, but was previously reported to be a common complication in children who had SBS. (41) A recent series reported five patients who had allergic colitis noted on flexible sigmoidoscopy or colonoscopy, although the composition of infant formula was not described. (30) The prevalence of colitis may be underestimated because colonoscopy is not performed frequently in infants who have SBS. This complication was found to improve with a reduction in the amount of formula administered and by administering sulfasalazine 25 to 50 mg/kg per day or prednisone 1 mg/kg per day. (41) The requirement for these anti-inflammatory treatments in infants who have SBS raises the question of whether chronic irritation of the colon can predispose to inflammatory bowel disease. Colonic irritation could result from bile acid malabsorption. Perhaps even more important, colonic inflammation and surface epithelial erosions are the consequence (in a piglet model) of excessive short-chain fatty acid concentrations and low luminal pH. (42) We have encountered two children who had SBS and eventually developed

inflammatory bowel disease, one with Crohn disease and the other with ulcerative colitis.

RENAL DISEASE. Most infants who have SBS have normal serum creatinine and urea nitrogen concentrations, and the latter can be a useful sign of dehydration. However, as the children become older, renal involvement can be seen. Kidney stones have been reported to occur in approximately 25% of adult patients who have SBS and a colon. The pathogenesis seems to involve hyperoxaluria resulting from calcium soap formation (association of malabsorbed fatty acids with calcium) and hyperabsorption of calcium oxalate from the colon. (43) However, stones in SBS patients also have been found to be formed from uric acid and ammonium acid urate. (44) Acute renal failure can be related to metabolic acidosis and dehydration. Long-term follow-up of adults receiving PN has documented a 3.5% annual reduction in creatinine clearance, mostly not attributable to aminoglycoside administration. (45) Focal renal tubulointerstitial fibrosis also has been reported in children and rats who have SBS and appears to result from arginine deficiency. (46) As with cholestatic liver disease, the harmful component of PN has not been identified.

MORTALITY. Of all the conditions encountered in neonatology and pediatric gastroenterology, SBS is associated with the highest morbidity and mortality. Recently, a large cohort of children from Michigan (n=80) was investigated. (47) SBS was associated with increased mortality if serum direct bilirubin was greater than 2.5 mg/dL (42.8 mcmol/L), with a relative risk of 23-fold ($P<0.05$), or if the percentage of normal small bowel length remaining (adjusted for postconceptual age) totaled less than 10%, with a relative risk of 5.7 ($P<0.003$).

In the study of approximately 12,000 infants from the United States Neonatology Research Network, the risk of surgical SBS was 1.1% of very low-birthweight infants, and the mortality rate in this group was 20%. (48) The risk factors for death with home PN were not studied. We have considerable experience with patients receiving home PN and suspect that important risk factors for mortality include young parental age, reduced support system ("social capital"), and illiteracy. We recommend that a major research agenda for government-sponsored research in developed countries should include research aimed at preventing premature delivery, preventing necrotizing enterocolitis (NEC), identifying the causes of congenital gastrointestinal anomalies, reducing mortality following small bowel transplantation, and improving the risks associated with chronic PN.

Surgical

The most pressing surgical complications are those related to maintaining central venous access. Frequently, multiple lines are removed because of septicemia or mechanical problems (eg, infants pulling out the lines). When most central veins are lost, unusual sites must be used, such as transhepatic lines inserted into hepatic veins. Early in the course of SBS, it is not unusual for children to develop enteric fistulae, especially infants who have NEC. In one 7-year study, 4% of 130 babies who had NEC developed this complication. (49) Fistulas are associated with strictures and septicemia and are diagnosed by contrast radiography.

Treatment

The primary goal of treatment in children who have SBS is facilitating intestinal adaptation while optimizing growth and development. Maximizing enteral feedings while minimizing PN is the major clinical dilemma facing any health-care professional taking care of children who have SBS and secondary intestinal failure.

Even though we are in the era of evidence-based medicine and have learned much over the past 2 decades about PN and intestinal adaptation, transitioning children from PN to enteral nutrition remains as much an art as a science. Figure 2 documents with a timeline some of the major advances in the treatment of pediatric SBS and some of the key clinician-investigators who made these contributions.

Parenteral Nutrition

It is not the purpose of this article to discuss PN formulation extensively. However, we underscore that PN has made possible long-term survival of children who have undergone major intestinal resection. (50)

Diet

For all children who have SBS, it is extremely important to establish enteral feedings as soon as medically possible. Initially, the potential "trophic effect" of enteral feedings is more important than the nutritional value of what can be accomplished enterally. In addition, enteral feedings may protect the liver from significant injury due to PN.

Starting human milk feedings as soon as possible is widely accepted as one important factor that may help the intestinal adaptation process. (51) Unfortunately, different issues affect the availability of human milk, such

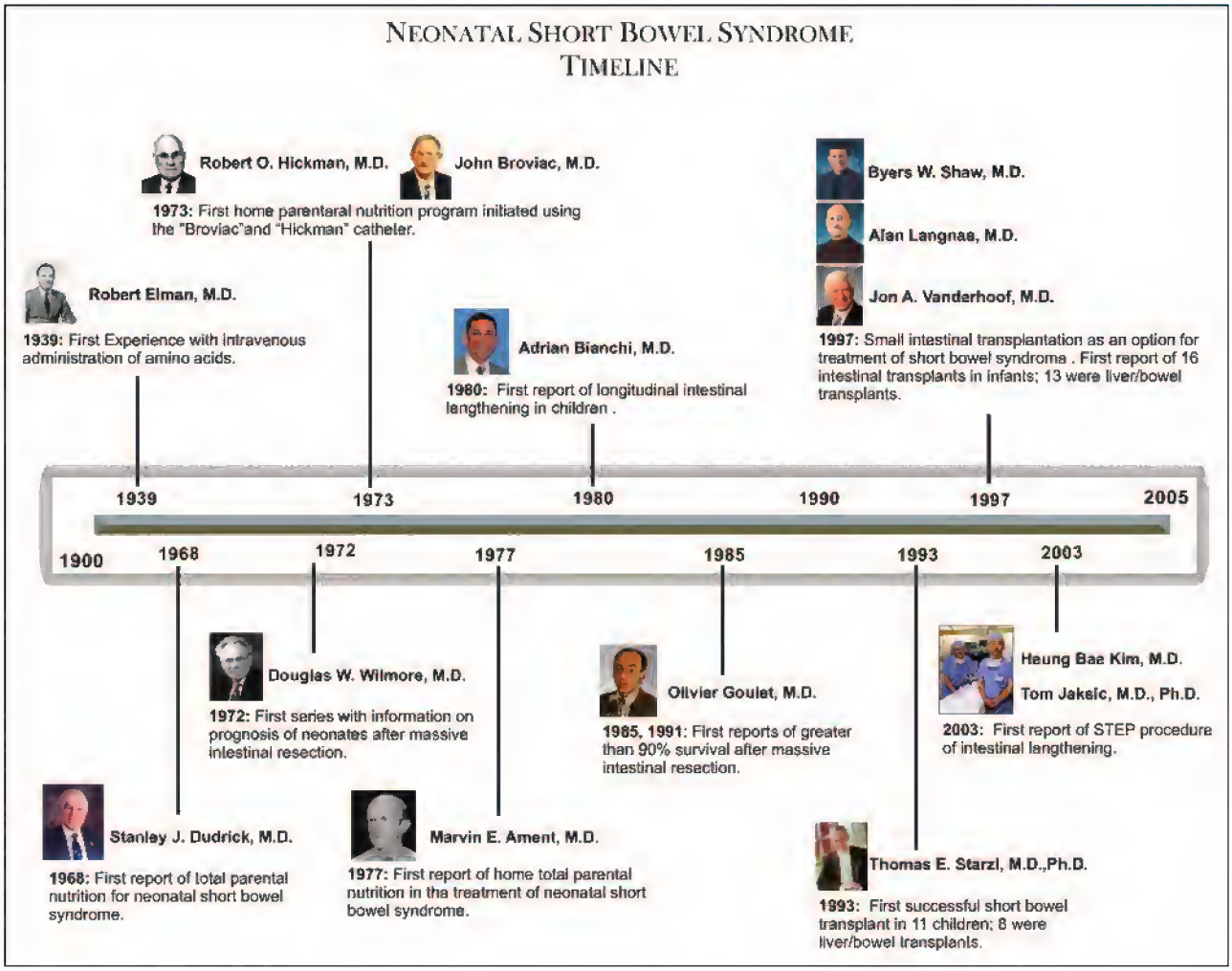

Figure 2. Timeline documenting some of the most important developments in the treatment of short bowel syndrome in infants. Several of the key contributors to the field are shown, although the list is not comprehensive. Note that the more recent surgical contributions are not yet "standard of care," and optimal bowel lengthening treatment is not defined. In addition, optimal transplant modality (liver versus intestine) for infants who are "stalled" or regressing with respect to bowel adaptation is not decided. Illustration by Nicole Fatheree, University of Texas Medical School, Department of Pediatrics, Division of Gastroenterology.

as inability for the baby to take the nipple, need for tube feedings, and need for pumping milk.

Most pediatric gastroenterologists recommend continuous feeding instead of bolus feedings because the infants may experience a vicious cycle of large-volume feeding and malabsorptive diarrhea. Therefore, gastrostomy tube placement should be considered in most cases. One study demonstrated that patients who had diarrhea showed an approximately 30% increase in absorption of fat, nitrogen, and trace elements with continuous feedings compared with bolus feeding. (50) On the other hand, bolus feedings are significantly more likely to produce gallbladder contractions, which may prevent gallstones. (33) Overall, no well-controlled studies have examined continuous versus bolus feeding. Therefore, the primary principle should be to use the method that allows the greatest proportion of enteral feedings.

It is also important to remember that patients receiving tube feedings may not develop good oropharyngeal coordination. Therefore, it is important to allow intake by mouth, even if this is small amounts. Our practice is to turn off the continuous infusion for 1 hour two to three times daily, at which times we provide an oral feeding equivalent to 1 hour of infused feeding.

One retrospective series showed that enteral feeding with human milk or an amino acid-based formula correlated with a shorter duration of PN requirement. (51) In general, the primary recommendation is to use elemental formulas when human milk is not available because most available studies have used human milk or elemental formulas for children who have SBS.

Animal studies in rats have shown that long-chain triglycerides (LCTs), especially menhaden oil, have a more significant trophic effect compared with diets containing short-chain or saturated fat. (52) One group recommends (for those patients who have colons) that 50% to 60% of calories be provided as complex carbohydrates, while fat is provided as both medium-chain triglycerides (MCTs) and LCTs along with oxalate restriction to reduce the risk of nephrolithiasis. (53) On the other hand, for those who do not have colons, approximately 50% of calories should come from complex carbohydrates, LCTs should be the sole source of fat, and no oxalate restriction is required. Both groups of patients should receive oral rehydration and soluble fiber. For children who have cholestasis, it is advisable to use high MCT-containing formula because bile is not required for MCT absorption.

Proteins are well absorbed in children who have SBS, probably because of lower concentrations in formulas and because of a large maximal velocity of peptide (di- and tripeptide) transporters and many different classes of amino acid transporters. It has been suggested that intact protein formula may not offer an advantage to elemental formula because children who have SBS may develop colitis that may be related to cow milk protein allergy. (41) Even though it was not clear if the colitis was due to cow milk protein allergy versus bile acid malabsorption in this study, it may not be a bad idea to eliminate the possibility of cow milk protein allergy when choosing the formula for these children.

Solid foods are believed to be well-tolerated, and we recommend initiation at the normal ages. Meats and complex carbohydrates (eg, potatoes and cooked vegetables) are well-tolerated. Refined carbohydrates such as candy bars and juices are discouraged.

Pharmacologic Treatment

HISTAMINE 2 BLOCKERS OR PROTON-PUMP INHIBITORS. Acid blockade has been recommended because of the hypergastrinemia stage and gastric and duodenal ulcers that are associated with SBS. (39)

URSODEOXYCHOLIC ACID AND OTHER CHOLERETICS. A choleretic (UDCA) is recommended for treatment or prevention of PN-associated liver disease because of its efficacy in other cholestatic conditions, such as gallstones and cystic fibrosis. Recently, a trial involving very low-birthweight infants showed that patients who received UDCA therapy at doses of 10 to 30 mg/kg per day had shorter durations of cholestasis than the control group (63 versus 92 days, P=0.006). (34) Furthermore, the peak serum concentration of direct bilirubin was significantly lower in the treatment group.

Attempts to reduce the severity of cholestasis with intravenous cholecystokinin have been largely unsuccessful. In a recent multicenter study in which 243 neonates were enrolled, cholecystokinin-octapeptide did not significantly affect direct bilirubin concentrations or secondary outcome measures, including the incidence of sepsis, time to achieve 50% or 100% of energy intake via the enteral route, number of intensive care unit and hospital days, mortality rate, or incidence of biliary sludge or cholelithiasis. (54)

BILE SALT RESIN BINDERS. The bile salt resin binder cholestyramine can produce a dramatic decrease in diarrhea. However, the benefit pertains only to those children who have suboptimal ileal bile salt absorption due to ileal resection. We use 240 mg/kg per day divided into three doses. Possible adverse effects are worsening of malabsorption in cases with extensive ileal resection, hyperchloremic acidosis, and reduced absorption of other drugs.

ANTIDIARRHEAL DRUGS. Loperamide (0.1 mg/kg per dose TID or QID) can be modestly helpful by decreasing intestinal transit time that results in increased capacitance of the gut and delay in the passage of fluid through the intestine, but it does not increase salt and water absorption directly. Fiber has been used to slow small bowel transit, although its use may lead to deterioration in children missing the colon or the ICV. Caution always should be exercised when using agents that decrease the intestinal transit because they may be associated with adverse effects such as ileus.

SBBO TREATMENT. Patients who develop SBBO are less likely to wean off PN. The organisms identified in bacterial overgrowth are often anaerobes or gram-negative bacteria. As a consequence of microbial proliferation within the duodenojejunum, intraluminal bile salts are deconjugated, resulting in failure of micellar solubilization and steatorrhea. In addition, these organ-

isms produce enzymes, such as elastase, that are known to reduce the activities of brush border digestive enzymes, such as lactase. (27) Based on these findings, it has been suggested that children who have SBS may benefit from cycles of oral antibiotics to treat or prevent bacterial overgrowth. Further studies in this area are needed to assess the potential benefit of this practice.

The use of probiotics in children who have SBS is controversial. Even though probiotics may be beneficial against bacterial overgrowth, there is always the concern of possible translocation, which has been reported in such children.

GLUTAMINE AND GROWTH HORMONE. Most elemental formulas based on amino acids rather than peptides have been enriched with high concentrations of glutamine (GLN). GLN is the primary metabolic fuel of the gut, a precursor of purines and pyrimidines, and a trophic "signal" to the enterocyte. In fact, GLN dosing activates mitogen-activated protein kinases (MAPKs) and enterocyte proliferation much in the same way that growth factors such as epidermal growth factor activate MAPKs and aid in their proliferation. (55)

Although GLN alone has not been shown to be effective in treating SBS, many trials have examined the combination of GLN, growth hormone (GH), and a high-carbohydrate/low-fat (HCLF) diet. A recent meta-analysis of GLN + GH (0.14 mg/kg per day) + HCLF diet, which included 13 controlled trials and 258 patients, showed that, compared with standard treatment, this combination had a beneficial effect on body weight, stool output, lean body mass, carbohydrate and nitrogen absorption, D-xylose absorption, and the ability to wean off PN. (56) Only a few pediatric patients have been treated, but GH (0.3 mg/kg per week subcutaneously) plus GLN (30 mg/day) was found to increase height percentile and seemed to facilitate PN independence. (57)

OTHER CONSIDERATIONS. Treatment of infants who have SBS with standard pediatric medications, such as antibiotics, is problematic because of erratic absorption. Therefore, intravenous medications should be considered when treating conditions such as otitis media.

Criteria for Discharge from Hospital

Parents or guardians must complete a comprehensive training period prior to patient discharge because they will assume full care and responsibility for central venous catheter care and PN administration at home. The major nutritional criterion for discharge from the hospital is evidence of steady weight gain on cycled PN and, in most instances, some enteral feedings. (21)

Monitoring

In the clinical setting, stool output and growth pattern are the primary factors related to decreasing the PN and increasing the enteral feedings. When growth is considered fully supported by enteral feedings, PN is stopped.

Weekly blood work should include but is not limited to: complete blood count and differential count, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, fractionated bilirubin, gamma-glutamyl transferase, albumin, creatinine, blood urea nitrogen, electrolytes, magnesium, calcium, and phosphorus. In addition to the weekly blood tests, we review an iron panel and prealbumin every month. We also check trace elements (zinc, manganese, selenium, copper, chromium) every 3 months. Vitamins A, D, E, and K are assessed every 6 months. Other tests to consider are vitamin B12, liver ultrasonography, renal ultrasonography, and bone mineral density testing.

Small Bowel Lengthening Procedures

The rationale behind lengthening procedures is to increase intestinal transit time and the subsequent intestinal absorptive capacity and potential for intestinal adaptation. The Bianchi procedure was the first intestinal loop lengthening technique for increasing small intestinal length, described in 1980. (58) In 2003, the serial transverse enteroplasty procedure (STEP) was described as an alternative for lengthening of the small bowel. (59) A recent study from Nebraska showed that both the Bianchi and STEP improve enteral nutrition, reverse complications of PN, and avoid intestinal transplantation in most patients. (60) Furthermore, there are reportedly few surgical complications. Because a dilated small bowel loop is required for either procedure, lengthening procedure should be considered only for those patients who have dilated loop of small bowel and are not steadily advancing in the intestinal adaptation process.

Transplantation

It is beyond the scope of this review to describe in detail liver or intestinal transplantation, but these procedures should be considered in certain children. Among potential candidates are those who have chronic intestinal failure and no hope for intestinal adaptation, those who have developed end-stage liver disease, those experiencing central line access problems, and patients who have recurrent central venous catheter-related septic episodes. More recently, isolated intestinal transplantation is emerging as a therapeutic option for children who have no hope for intestinal adaptation (ie, ultra-short bowel syndrome in which the remaining bowel totals less than

15 cm, absence of the ICV, or long-segment Hirschsprung disease).

Remaining Questions

The major unresolved questions and issues include PN-associated liver disease; osteopenia; renal disease; and nutritional, medical, and surgical interventions that may promote the intestinal adaptation process. Questions related to enteral nutrition include:

- Which is the optimal lipid source: LCT or a combination with MCT?
- Is amino acid formula preferred to formulas with casein (or whey) hydrolysate when human milk is not available?

Questions related to PN include:

- Are omega-3 fatty acids or a combination of omega-3 and omega-6 fatty acids the optimal lipid emulsion?
- Should amino acids be modified (eg, including citrulline)?

Questions related to surgical options include:

- What is the optimal surgical management for patients with NEC? Although use of peritoneal drains may minimize the length of intestine removed, this approach has been reported to be associated with neurodevelopmental problems.
- For bowel lengthening, is the Bianchi procedure or the STEP safer and more effective?

SBS continues to reign as perhaps the most deadly and most costly illness of the pediatric gastroenterology service at most tertiary care centers that have large neonatal intensive care units. The costs are not only financial, but also emotional, social, and medicolegal. Continued surgical and medical research undoubtedly will improve the outlook for affected babies.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the clinical features, complications, and management of short gut syndrome.
- Recognize the association of cholestasis with total parenteral nutrition, know how to manage this, and understand how to diagnose other possible causes.
- Recognize the causes and clinical manifestations of catheter complications of parenteral nutrition.

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NeoReviews Quiz

7. Central line infections are common among infants who have SBS and are hospitalized, as well as among those receiving home parenteral nutrition. Of the following, the *least* common organism associated with central line sepsis in infants who have SBS, based on the experience of Navarro and associates, is:

   A. *Candida.*
   B. *Enterococcus faecalis.*
   C. *Klebsiella.*
   D. *Staphylococcus "nonaureus."*
   E. *Streptococcus viridans.*

8. Cholestatic liver disease is a frequent complication of long-term administration of parenteral nutrition to infants who have SBS. Several studies have attempted to identify the injurious factor in the parenteral nutrition solution that triggers the cholestasis. Of the following, the nutrient *most* likely to be injurious to the liver is:

   A. Copper.
   B. Cysteine.
   C. Selenium.
   D. Taurine.
   E. Zinc.

9. In addition to central line sepsis and cholestatic liver disease, several other complications can occur in infants who have SBS. Of the following, the *most* common complication is:

   A. Allergic colitis.
   B. Central vein thrombosis.
   C. Gallstones.
   D. Gastric ulcer.
   E. Small bowel bacterial overgrowth.

Core Concepts:
Respiratory Distress Syndrome

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Author Disclosure
Drs Warren and Anderson have disclosed no financial relationships relevant to this article. This commentary does not include a discussion of an unapproved/investigative use of a commercial product/device.

Objectives
After completing this article, readers should be able to:

1. Define respiratory distress syndrome (RDS).
2. Discuss the epidemiology, pathophysiology, and diagnosis of RDS.
3. Create a differential diagnosis for respiratory distress in the neonate.
4. Describe the proven treatments for RDS, with particular attention to antenatal steroids and surfactant replacement therapy (SRT), their benefits and possible complications.
5. Discuss ventilation strategies that can be used in the infant who has RDS.
6. Describe long-term complications of RDS and its treatments.

Abstract
Respiratory distress syndrome (RDS) is seen primarily in the preterm neonate and is due mostly to pulmonary surfactant deficiency. Lung atelectasis leads to ventilation-perfusion mismatching, hypoxia, and eventual respiratory failure in the untreated infant who has RDS. RDS is diagnosed by physical findings consistent with respiratory distress and characteristic radiographic findings. Treatment of RDS begins antenatally with the administration of maternal steroids to women at risk of preterm delivery between 24 and 34 weeks' gestation. The use of repeat doses of antenatal steroids is under investigation but is currently not recommended outside of randomized, controlled trials. SRT has been approved for use since 1990 and has been successful in decreasing rates of RDS. Natural surfactant is currently recommended for use, but synthetic surfactant that contains proteins to mimic surfactant proteins is being investigated. In general, prophylactic use of surfactant is recommended over rescue treatment in infants at high risk for developing RDS, but the determination of which infants are at high risk for developing RDS remains a clinical one. The push toward use of less invasive ventilation strategies in the treatment of RDS has led to several trials of nasal continuous positive airway pressure (nCPAP). Results of the SUPPORT trial are pending, but the COIN trial has concluded that nCPAP use in infants who have RDS is not detrimental. Inhaled nitric oxide for RDS still requires investigation on safety and efficacy. Several other treatments have been studied, but as of yet, only inositol administration shows promise in the treatment of RDS. Several complications of the recommended treatments for RDS have been identified, but the benefits far outweigh the risks. Finally, there remains a need for long-term follow-up studies on preterm infants treated for RDS to assess neurodevelopmental outcomes.

Definition
RDS, formerly known as hyaline membrane disease, occurs in incompletely developed lungs and is, therefore, a disease of prematurity. Immature lungs are functionally deficient in mature surfactant. (1) The absence of surfactant in the liquid film lining of alveoli causes an increase in surface tension and alveolar collapse. (2) If not treated, such atelectasis causes an increased work of breathing, intrapulmonary shunting, ventilation-perfusion mismatch, hypoxia, and eventual respiratory failure. (1)

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Epidemiology

RDS is seen almost exclusively in preterm infants, before the lungs begin to manufacture adequate amounts of surfactant. (2) In fact, the risk of RDS decreases with increasing gestational age: 60% of babies born at fewer than 28 weeks' gestation, 30% of babies born between 28 and 34 weeks' gestation, and fewer than 5% of babies born after 34 weeks' gestation develop RDS. (3) Other factors that increase the risk of RDS include male sex, maternal gestational diabetes, perinatal asphyxia, hypothermia, and multiple gestations. (4) Antenatal steroids and prolonged rupture of membranes decrease the risk of RDS. (5) With the advent of therapies for RDS, including antenatal steroids and SRT, mortality from RDS has decreased from nearly 100% to less than 10% in recent years. (6)

Differential Diagnosis

The differential diagnosis of respiratory distress in the newborn encompasses upper respiratory obstruction, pulmonary disease, cardiac disease, thoracic causes, metabolic disorders, diaphragmatic causes, neuromuscular diseases, infectious causes, hemolytic/vascular causes, and miscellaneous causes (Table 1). (7)(8)

Pathophysiology

Normal Lung Development

The period of viability begins at around 23 weeks' gestation, when the fetal lung begins to transition from the canalicular to the saccular stage of development (Table 2). (9) During the saccular stage, peripheral airways enlarge and distal airways begin to dilate while their walls begin to thin. (10) Type II pneumocytes, the cells responsible for surfactant production, are present and maturing. (10) Although gas exchange is possible during this stage, total surface area for gas exchange is low and diffusion distance for gas exchange is high in relation to body weight and metabolic rate. (9) Secondary septation, or alveolarization, begins at about 32 weeks' gestation. (9) During this phase, alveoli form and mature and alveolar walls thin. (10) All cell types proliferate during this phase, including type II pneumocytes. (10) The overall result is a maturing lung with a larger surface area and a minimal diffusion distance for gas exchange. (10)

Surfactant Composition and Life Cycle

Surfactant is a mixture of phospholipids and proteins. (2) The most abundant surface-active phospholipid in mature lungs is phosphatidylcholine. (11) Phosphatidylcholine forms a monolayer on the liquid film lining of the alveolus, lowering the surface tension of that film. (2) In addition to phospholipids, surfactant contains four major proteins: surfactant proteins (SPs) A, B, C, and D (Table 3). (11) SP-A helps to regulate surfactant secretion and uptake; SP-B and SP-C facilitate adsorption and spreading of phospholipids on the liquid film lining of the alveoli. (2) SP-D may play a role in surfactant reuptake and recycling. (5)

Pulmonary surfactant is manufactured in the Golgi apparatus and stored in lamellar bodies of type II pneumocytes. (5) Once secreted by the lamellar bodies into the extracellular space, surfactant is organized into tubular myelin, adsorbed into the air-water interface, and formed into a lipid monolayer. (5)(6) The surface-active properties of the lipid monolayer decrease the surface tension of the air-water interface and prevent alveolar collapse. (6) The majority of surfactant constituents are believed to be recycled, either through reuptake by type II pneumocytes or by alveolar macrophages. (9)

RDS

An infant born before the alveolarization stage of lung development has underdevelopment of alveolar sacs and difficulty with oxygenation and ventilation. (9) Similarly, an infant born before this stage of lung development experiences a delay in production and secretion of functional surfactant. (9) Such surfactant deficiency is the major reason for poor lung function in the preterm neonate (Table 4). (2)

Although the preterm neonate does produce a small amount of surfactant, this surfactant contains low amounts of phospholipids and SPs. (9) It is estimated

Abbreviations

AT:	antithrombin
BPD:	bronchopulmonary dysplasia
CLD:	chronic lung disease
FRC:	functional residual capacity
GBS:	group B *Streptococcus*
iNO:	inhaled nitric oxide
IVH:	intraventricular hemorrhage
nCPAP:	nasal continuous positive airway pressure
NIH:	National Institutes of Health
NIMV:	nasal intermittent mandatory ventilation
PIE:	pulmonary interstitial emphysema
PVL:	periventricular leukomalacia
RDS:	respiratory distress syndrome
SP:	surfactant protein
SRT:	surfactant replacement therapy

Table 1. Differential Diagnosis of Respiratory Distress in the Newborn

Upper Airway Obstruction
Choanal atresia, nasal stenosis, Pierre Robin sequence, laryngeal stenosis or atresia, hemangioma, vocal cord paralysis, vascular rings, tracheobronchial stenosis, masses, cleft palate, nasal stuffiness
Pulmonary Diseases
Respiratory distress syndrome, retained fetal lung liquid syndrome (transient tachypnea of the newborn), aspiration (including meconium aspiration syndrome), pneumonia, pneumothorax, pneumomediastinum, primary pulmonary hypertension, tracheoesophageal fistula, pulmonary hemorrhage, pulmonary hypoplasia, pulmonary agenesis, cystic disease, pleural effusion, chylothorax, neoplasm, bronchopulmonary sequestration, pulmonary arteriovenous malformation, pulmonary interstitial emphysema, pulmonary edema, congenital alveolar proteinosis, congenital lobar emphysema
Cardiac Diseases
Cyanotic congenital heart disease, acyanotic congenital heart disease, arrhythmia, increased intravascular volume, high output failure, pneumopericardium, cardiomyopathy
Thoracic Causes
Chest wall deformity, mass
Metabolic Disorders
Hypoglycemia, infant of a diabetic mother, inborn errors of metabolism
Diaphragmatic Causes
Hernia, paralysis
Neuromuscular Diseases
Central nervous system damage (birth trauma, hemorrhage), medication (maternal sedation, narcotic withdrawal), muscular disease (myasthenia gravis), intraventricular hemorrhage, meningitis, hypoxic-ischemic encephalopathy, seizure disorder, obstructed hydrocephalus, infantile botulism, spinal cord injury
Infectious Causes
Sepsis, pneumonia (especially group B *Streptococcus*)
Hemolytic/vascular Causes
Anemia, polycythemia, abnormal hemoglobin
Miscellaneous Causes
Asphyxia, acidosis, hypo/hyperthermia, hypo/hypernatremia

that infants who have RDS have surfactant pools of less than 10 mg/kg compared with pools of up to 100 mg/kg in term infants. Such surfactant deficiency necessitates increased work of breathing to distend alveoli, which the preterm neonate may not be able to provide. (2) Diffuse atelectasis ensues and leads to an overall decrease in functional residual capacity (FRC) of the lungs. (2) If an infant is allowed to breathe from an inadequate FRC, lung injury can occur. (9) Lung injury leads to protein exudation and edema, which can inactivate surfactant further. The acidosis and hypoxia that results from atelectasis and lung injury further interferes with surfactant production. The combination of these events leads to respiratory failure.

Diagnosis

Clinical Evaluation

RDS presents at the time of or soon after birth, and symptoms worsen over time. (2) Clinical symptoms of RDS are the same as those of any other respiratory distress: tachypnea, nasal flaring, chest wall retractions, expiratory grunting, and central cyanosis. (2) In the extremely preterm infant, the only clinical symptom of RDS may be apnea. (2) It is important to remember that some infants who have RDS exhibit all of these symptoms, and others may show none.

An accurate history is important in diagnosing RDS. As stated, RDS is more prevalent in earlier gestational ages, so an accurate estimation of gestational age is necessary. Other historical factors must be discerned, such as antenatal steroid therapy; maternal history of gestational diabetes; course of labor, including prolonged rupture of membranes, maternal fever, group B *Streptococcus* (GBS) status and antibiotic therapy; method of delivery; and need for resuscitation.

Diagnostic Studies

Along with the history and physical examination, a chest radiograph is needed for the diagnosis of RDS. The typical chest radiograph shows diffuse atelectasis and the classic "ground glass" appearance of the lung fields (Figure). (2) Air bronchograms, which are air-filled bronchi superimposed on the relatively airless parenchyma of the lung tissue, also are seen commonly on chest radiograph. (2) Importantly, the appearance of GBS pneumonia on

Table 2. Normal Lung Development (10)

Phase	Embryonic	Pseudoglandular	Canalicular	Saccular	Alveolar
Gestation (weeks)	~0 to 7	~7 to 17	~17 to 27	~28 to 36	~36+
Structures	Trachea and bronchi	Conducting airways and terminal bronchioles	Respiratory bronchioles, alveolar ducts, primitive alveoli	Enlarged peripheral airways, thinned alveolar walls	Definitive alveoli
Type II Pneumocytes	Absent	Immature; undifferentiated	Immature; differentiated	Developing laminar bodies	Mature

chest radiograph can be identical to that of RDS. (12) Empiric antibiotics to address GBS infection should be started until such disease is ruled out. Arterial blood gas measurements show hypercarbia and hypoxia and eventually, in the unsupported infant, metabolic acidosis. (2) In all, a preterm infant must have clinical signs of respiratory distress and a classic chest radiograph to be diagnosed with RDS. (2)

Management

Antenatal Steroids

Antenatal steroid administration to women at high risk of preterm delivery prior to 34 weeks' gestation has been standard of care since the 1994 National Institutes of Health (NIH) Consensus Conference. (13) A Cochrane review by Roberts and Dalziel from 2006 confirmed the benefits of antenatal steroids, which include decreases in neonatal death, intraventricular hemorrhage (IVH), and RDS. (1) Antenatal steroids are believed to decrease the incidence of RDS by accelerating maturation of the fetal lung. (13)

Early studies on the use of antenatal steroids did not include data on babies who were delivered before 28 weeks' gestation, so there was a question of whether antenatal steroids would be beneficial in this age group. The Roberts and Dalziel review shows that when steroids are administered initially at 26 weeks' gestation, there is a decreased incidence of RDS that is not seen if steroids are administered before 26 weeks' gestation. (1) However, the incidence of IVH still may be reduced if steroids are administered at fewer than 26 weeks' gestation. (1) Therefore, because of the apparent benefit to preterm infants in terms of decreased IVH, antenatal corticosteroid administration is recommended for preterm infants starting at 24 weeks' gestation. (13)

Both betamethasone and dexamethasone have been studied and found to be more effective than placebo, but these steroids have not been examined head-to-head. (13) The Roberts and Dalziel review suggests that betamethasone may cause a larger reduction in RDS than dexamethasone. (1) Baud and colleagues (14) found that antenatal exposure to betamethasone, but not dexamethasone, is associated with a decreased risk of periventricular leukomalacia (PVL) in preterm infants, but there is no difference in the incidence of cerebral palsy. (1) With this limited evidence, two doses of betamethasone administered 24 hours apart is currently the recommended steroid for antenatal use. (13)

Antenatal steroid administration has been shown to be beneficial if provided fewer than 24 hours before

Table 3. Surfactant Proteins and Their Functions (5)

Surfactant Proteins	Functions
SP-A	Part of the host innate immune defense Facilitates the formation of tubular myelin Regulates surfactant secretion and uptake
SP-B	Promotes adsorption and spreading of pulmonary surfactant
SP-C	Promotes adsorption and spreading of pulmonary surfactant
SP-D	Part of the host innate immune defense May play a role in pulmonary surfactant reuptake and recycling

Table 4. Results of Surfactant Deficiency (2)

1. Decreased lung compliance
2. Unstable alveoli
3. Decreased functional residual capacity
4. Hypoxia (from shunting of blood through atelectatic portions of the lung)
5. Increased work of breathing
6. Lung edema (exudation of fluid and serum proteins)

Figure. Classic chest radiograph in an infant who has RDS.

delivery. Therefore, steroid administration is recommended before delivery of preterm infants 24 to 34 weeks' gestation unless delivery is imminent. (13) Furthermore, a reduction in RDS has been seen in infants born up to 7 days after the first dose of antenatal steroids was administered. (1) No benefit is seen in infants who receive the first dose of steroids more than 7 days before birth. (1)

Because antenatal steroids seem to be of benefit only when administered from just before birth to 7 days before delivery, the utility of repeated antenatal steroid dosing has been studied. The latest Cochrane review on the subject, conducted by Crowther and Harding in 2007, suggests that repeat doses of prenatal steroids do reduce the incidence and severity of neonatal lung disease in the first few postnatal weeks. (15) They recommend repeat doses of corticosteroids in women at risk for preterm birth when the first course of steroids was administered more than 7 days previously because of the short-term benefits to the fetal lungs. They do, however, warn about the possibility of decreased birthweight and head circumference at birth, which has been reported. For example, repeat antenatal steroid courses in fetal sheep result in increased lung maturation as well as increased growth restriction. (13) Guinn and colleagues (16) showed that the composite neonatal morbidity, including severe RDS, bronchopulmonary dysplasia (BPD), severe IVH, PVL, sepsis, necrotizing enterocolitis, or perinatal death, was not reduced by using weekly courses as compared with one course of antenatal steroids. Because the true risk-to-benefit ratio of using repeat doses of antenatal steroids is not known, the 1994 and 2000 NIH Consensus Conference recommends the use of repetitive courses of steroids only in the context of randomized, controlled trials (Table 5). (13)

Surfactant

SRT was approved for use by the United States Food and Drug Administration in 1990. (5) Immediate improvement in oxygenation, along with improved aeration on chest radiograph within 1 hour, is seen after administration of SRT. (5)(17) SRT reduces the incidence of RDS, death, pneumothorax, pulmonary interstitial emphysema (PIE), and IVH in preterm infants. (17) Although most available evidence suggests that SRT increases survival rates without increasing the risk of disability, the risk of long-term disability is unknown due to few reported

Table 5. Summary of 1994 and 2000 National Institutes of Health Consensus Conference Antenatal Steroid Recommendations

1. The benefits of prenatal corticosteroids outweigh any risks that have been identified. The benefits include decreased death and decreased incidence of respiratory distress syndrome and intraventricular hemorrhage.
2. All fetuses at 24 to 34 weeks' gestation are candidates for corticosteroid therapy.
3. Prenatal corticosteroid therapy should be used without consideration of fetal sex, race, or the availability of surfactant treatments for respiratory distress syndrome.
4. Prenatal corticosteroids should be administered if tocolytics are used.
5. Because of probable benefit for treatment to delivery intervals of less than 24 hours, prenatal corticosteroids are indicated unless delivery is imminent.
6. Repeated courses of corticosteroids may not be safe and should not be administered outside of clinical trials.

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follow-up studies on the preterm infants who have received surfactant. (17)

Surfactant is administered directly into the lungs via an endotracheal tube. (5) Other methods of surfactant administration, including aerosolization, nebulization, and instillation via bronchoalveolar lavage, have been found to be ineffective. (5) Surfactant administration via laryngeal mask airway is being studied. (5) Surfactant can be administered as either two or four fractional doses in either two or four different body positions; clinical evidence is not sufficient to recommend an optimal number of fractional doses. (17) Surfactant can be administered as either a bolus or an infusion into the endotracheal tube; again, data in humans are insufficient to recommend an optimal method of surfactant administration. (17) Interestingly, data examining the distribution of surfactant in mechanically ventilated rabbits showed that bolus instillation resulted in reasonably homogenous pulmonary surfactant distribution, while tracheal infusion resulted in extremely uneven pulmonary distribution. (18)

Natural and synthetic surfactant preparations exist, and both are effective in the treatment and prevention of RDS. (19) Natural surfactants are derived from animal lungs (bovine or porcine) and contain phospholipids with SP-B and SP-C; first-generation synthetic surfactants contain only phospholipids without proteins. (19) A Cochrane meta-analysis by Soll and Blanco conducted in 2001 comparing natural surfactant to first-generation synthetic surfactant confirmed that natural surfactant more effectively reduces the risk of pneumothorax and lowers mortality rates in infants treated for RDS. (20) There is also a marginal decrease in the risk of BPD when using natural surfactant. Although natural surfactants appear to be associated with higher rates of IVH, grade 3 and 4 IVH rates are not increased. The conclusion of this meta-analysis is that natural surfactants are the more desirable choice over the first-generation synthetic surfactants, which is likely due to the inclusion of the SPs in the natural surfactant. (20)

Synthetic surfactants containing peptides that mimic SPs recently have been developed and tested. (21) In a meta-analysis of two studies comparing protein-containing synthetic surfactant to natural surfactant, no statistically significant differences were found between the two groups in terms of death or chronic lung disease (CLD), and clinical outcomes were generally similar. (21) Further studies comparing these two groups are needed.

The use of prophylactic versus selective administration of surfactant has been studied thoroughly. Prophylactic SRT involves intubation and surfactant administration in preterm infants at high risk for RDS and usually occurs after the initial resuscitation and within 10 to 30 minutes of birth. (17) Prophylactic SRT has the advantage of establishing a normal surfactant pool before damage due to a low FRC, and an increased work of breathing can occur. (5) Its major disadvantage is the possibility that an infant who would not have developed RDS may be intubated and treated with surfactant. (5) Selective, or rescue, SRT is the administration of surfactant to preterm infants who already have developed RDS. (17) The two types of selective SRT are early and late. (17) Early selective SRT is administered within 1 to 2 hours of birth; late selective SRT occurs 2 or more hours after birth. The advantage of selective SRT is the avoidance of overtreatment, but in those infants who develop RDS, the delay in treatment allows lung inflammation and damage to occur. (5)

In the Cochrane review by Soll and Morley in 2001, the use of prophylactic surfactant in infants at high risk of developing RDS was compared with selective surfactant treatment at the time of respiratory failure. (22) Prophylactic surfactant treatment was associated with a significant reduction in the risk of pneumothorax, PIE, mortality, and BPD or death. (22) A secondary analysis of infants of fewer than 30 weeks' gestation found a significant decrease in the risk of mortality and the risk of BPD or death. The conclusion of this study is that prophylactic surfactant is beneficial in preterm infants believed to be at high risk for developing RDS, but the best method of determining if an infant is at high risk for developing RDS remains unclear. (22)

Because the incidence of RDS decreases with increasing gestational age, it becomes likely that prophylactic treatment with surfactant once gestational ages approach 28 to 30 weeks results in a good percentage of overtreatment. (5) In these cases, it may make more sense to treat selectively with surfactant. The most recent Cochrane review examining early versus late selective surfactant administration found that early selective SRT decreased neonatal mortality, pneumothoraces, PIE, and the incidence of CLD and death at 36 weeks' postmenstrual age when compared with late selective SRT. (5)

Finally, in 1999, a Cochrane review compared multiple versus single doses of natural surfactant for the treatment of RDS. (23) The reason for this comparison was the observation that some infants seemed to relapse after initial surfactant treatment. In this meta-analysis, a more sustained response in the treatment of RDS was seen in the group of infants allowed to have multiple doses of surfactant. (23) A decreased risk of pneumotho-

rax and a trend toward a decreased risk of mortality also was reported.

Overall, survival without BPD has increased since SRT began, although the incidence of BPD in very low-birthweight infants is unchanged. (17) The risk of respiratory problems later in infancy or childhood (including asthma and infection) remains high for preterm infants who were treated with surfactant and mechanical ventilation. (17) Long-term studies are needed to assess the respiratory function of children who received surfactant as preterm infants. (17)

Antenatal Steroids and Surfactant

No randomized, controlled trials have been conducted to address whether antenatal steroids reduce the need for prophylactic or rescue SRT in preterm infants. (17) On subgroup analyses of observational studies and clinical trials, infants born before 32 weeks' gestation who received both antenatal steroids and SRT had significant reductions in mortality, severity of respiratory distress, and frequency of air leaks compared with infants who received neither treatment, only antenatal steroids, or only SRT. (17) Infants born before 27 weeks' gestation did not have a lower incidence of RDS, but the severity of RDS may have been decreased. Therefore, it is generally accepted that the effects of antenatal steroids and SRT are additive, and it is not expected that trials will be conducted to verify this.

Ventilatory Management

Several methods can be used to ventilate the preterm neonate at risk for RDS. Surfactant administration followed by conventional ventilation has historically been the management of choice, but concerns that both positive pressure ventilation via the endotracheal tube and the duration of mechanical ventilation have direct effects on the incidence of BPD have prompted investigators to search for less harsh ventilatory strategies. (24)(25) Because most preterm infants who have RDS require ventilatory support and BPD is a major morbidity of many forms of ventilatory support, the hope is to find a noninvasive method of ventilation for RDS that is both safe and effective.

The initial belief was that more complex ventilation strategies, such as high-frequency oscillatory ventilation, might decrease the risk of developing BPD. However, when optimal lung volume strategies are used, there is no difference between conventional ventilators and high-frequency ventilators in terms of pulmonary and nonpulmonary outcomes. (24)(25) A Cochrane review on this subject from 2007 confirmed the lack of clear evidence for elective use of high-frequency ventilation over conventional ventilation because no difference was documented in mortality between the two modes of ventilation at 30 days or at term-equivalent age. (26) Patient-triggered ventilation is a form of conventional ventilation that includes synchronized intermittent mandatory ventilation, assist control, and pressure support. (24)(25) Studies have shown that patient-triggered ventilation has benefits over conventional ventilation and high-frequency ventilation in terms of a decreased duration of mechanical ventilation and decreased number of days on oxygen. (24)(25) However, there was no significant difference in terms of a decrease in lung injury between the three ventilation strategies.

The noninvasive ventilation strategy of nCPAP is believed to work by improving oxygenation without increasing $PaCO_2$ through the stabilization and recruitment of collapsed alveoli. (27) The idea is that nCPAP will help to achieve the adequate FRC that is necessary to avoid the development of RDS because increased FRC means increased alveolar surface area and less intrapulmonary shunt. (27) The avoidance of endotracheal intubation saves the infant from the barotrauma and volutrauma seen with the use of mechanical ventilators. A Cochrane Review from 2002 states that although a higher rate of pneumothorax was seen, there was an overall reduction in respiratory failure and mortality in preterm infants who had RDS and were treated with nCPAP. (28) Large randomized, controlled trials to evaluate this possibility are underway.

The COIN trial (Continuous Positive Airway Pressure or Intubation at Birth) is a recently published randomized trial addressing whether the use of nCPAP shortly after birth would decrease the rates of death and BPD (defined as the need for oxygen at 36 weeks gestational age). (29) A total of 610 infants from gestational ages 25 to 28 and 6/7 weeks were randomized at 5 minutes after birth to receive either nCPAP or intubation and mechanical ventilation. Outcomes between the two groups were assessed at 28 days, 36 weeks gestational age, and before discharge. There was a significantly lower risk of death or need for oxygen at 28 days in the nCPAP-treated infants, but early nCPAP did not significantly decrease the rates of death or BPD compared with intubation and ventilation at 36 weeks gestational age. Infants in the nCPAP group required fewer overall days of ventilation, but also had a significant increase in pneumothoraces compared with mechanically ventilated infants. The overall conclusion of the study was that early

nCPAP was not detrimental to preterm infants whose gestational ages were between 25 and 28 and 6/7 weeks. (29)

The SUPPORT trial (Surfactant Positive Airway Pressure and Pulse Oximetry Trial in Extremely Low Birthweight Infants) is currently ongoing. This trial is randomizing infants of gestational ages between 24 weeks and 27 and 6/7 weeks to either a treatment group of CPAP and permissive ventilation management or a control group of prophylactic/early surfactant and conventional ventilator management as well as either a low (85% to 89%) or high (91% to 95%) SpO_2 group. Results of this study are pending. (30)

Finally, nasal intermittent mandatory ventilation (NIMV) has been studied in the treatment of RDS. The rationale for NIMV use is that the administration of "sighs" to the neonate can help to open microatelectasis and recruit more alveoli. (31) Kugelman and associates (31) showed that NIMV was more successful than nCPAP in the initial treatment of RDS among infants younger than 35 weeks' gestation by reducing the rate of endotracheal intubation and the incidence of BPD. (31) As with other studies, failure of nasal respiratory support was associated with lower birthweight. Further study is needed, but NIMV may be a promising noninvasive method of ventilation for preterm infants at risk for RDS.

Ventilatory Management and Surfactant

Surfactant is a proven treatment for RDS that must be administered via endotracheal tube. As ventilation strategies become more sophisticated and less invasive, the use of surfactant may become more complicated. The push toward less invasive ventilation strategies does not allow an opportunity for surfactant administration. To allow for use of surfactant, many centers have started to intubate, administer surfactant, and extubate to minimally invasive respiratory support ("in-and-out surf"). A recent Cochrane Review compared early surfactant administration with brief ventilation to selective surfactant with continued mechanical ventilation in preterm infants who had or were at risk for RDS. (32) The use of surfactant followed by early extubation to nCPAP was more effective than selective intubation and surfactant administration followed by mechanical ventilation in preventing the need for mechanical ventilation as well as decreasing the incidence of BPD and pneumothorax. (32) No investigators currently are examining the use of early and continuous nCPAP versus surfactant administration followed by early extubation and nCPAP.

Inhaled Nitric Oxide (iNO)

NO is a vascular endothelial relaxing factor that successfully causes local smooth muscle cell relaxation in the pulmonary circulation when delivered by inhalation. (33) iNO has been used as a treatment in illnesses in which pulmonary vasodilation would be of benefit. Pulmonary hypertension is recognized as a complicating factor that may contribute to RDS. (33) The ability of iNO to dilate the blood vessels in the pulmonary vasculature, reduce pulmonary hypertension, and improve ventilation-perfusion matching (a known problem in RDS) has led to clinical trials on the use of iNO in the preterm infant who has RDS. (33) Of note, one major concern for the use of iNO in preterm infants is the adverse effect of bleeding complications.

In the Cochrane Review conducted by Barrington and Finer in 2007, iNO possibly improved outcome in mildly ill infants, with a possible decrease in ICH. (34) However, when administered to very ill preterm infants, iNO did not improve outcome and may have contributed to an increase in ICH. (34) Overall, the benefit of iNO in the preterm infant is largely unknown, and further randomized, controlled trials with subsequent meta-analyses are needed to answer this question. (33)

Other

Several other therapies have been studied as possible treatments for RDS. The following therapies have been reviewed in meta-analyses and published in the Cochrane Database of Systematic Reviews.

DIURETICS. RDS may be complicated by lung edema, so studies have been performed to determine if administration of diuretics may improve the course of RDS. A Cochrane Review by Brion and Soll in 2007 (35) analyzed seven studies with the aim of assessing risks and benefits of diuretic use in preterm infants who had RDS. Six of these studies used furosemide and were conducted before the era of prenatal steroids and surfactant. Although a transient furosemide-induced improvement in pulmonary function was seen, this benefit did not outweigh the risk for patent ductus arteriosus and hemodynamic instability. There were no long-term benefits. The other study assessed theophylline use and found no long-term benefits. Overall, the reviewers of these studies did not find data to support the routine administration of furosemide or theophylline in preterm infants who had RDS. (35)

ANTITHROMBIN (AT). AT is produced by the liver and is important in both blood clotting and clot lysis. Infants

who have RDS, as well as infants who have other critical illnesses, have low serum AT concentrations. It was hypothesized that increased thrombin formation due to low AT concentrations might contribute to the pathophysiology of RDS and that administration of AT may improve the clinical course of affected infants. A review by Bassler and associates (36) found a trend toward increased mortality as well as a significantly prolonged duration of mechanical ventilation and oxygen therapy in the AT-treated group. Therefore, due to the lack of benefit, as well as the potential harm, AT is not a recommended treatment for infants who have RDS.

DIGOXIN. It has been suggested that pulmonary edema due to congestive heart failure may contribute to RDS in the neonate. Based on this suggestion, digoxin has been studied as a potential treatment in RDS. Two randomized, controlled trials were analyzed by Soll, (37) who found that digoxin did not result in improved RDS symptoms. Therefore, digoxin is not recommended for use in infants solely affected with RDS.

INOSITOL. Inositol is a nutrient required by cells for growth and survival that also has been found to promote maturation of several components of surfactant. A 2003 review by Howlett and Ohlsson (38) includes three randomized, controlled trials of the use of inositol in preterm infants who had RDS. A significant reduction in death or BPD, stage 4 retinopathy of prematurity, and grade 3 or 4 IVH was seen in the inositol-treated group. No significant increase in adverse effects was reported. Due to the relatively small number of infants in these reviewed trials, multicenter randomized, controlled trials are recommended. However, these early results on the use of inositol in preterm infants with RDS are promising.

POSTNATAL THYROID HORMONE. Animal research has shown that antenatal administration of thyroid hormone stimulates surfactant production and reduces the incidence and severity of RDS. A review by Osborn and Hunt (39) examined trials that used postnatal thyroid hormone in preterm infants who had RDS. The conclusion was that administration of thyroid hormone therapy within the first hours after birth had no significant effect on the severity of RDS, morbidity, or mortality in such preterm infants and, therefore, is not recommended.

Complications and Treatment of RDS

A major pulmonary complication of RDS is the development of BPD, which is generally defined as the need for oxygen supplementation at 36 weeks' corrected gestational age. (11) Importantly, BPD is not caused by RDS; rather, it can be the result of the many treatments of RDS. (40) The "new BPD," a term coined by Jobe in 1999, describes a syndrome that results from processes that interfere with lung development, not a syndrome resulting only from injury. (40) These processes can include chorioamnionitis, oxygen administration, high tidal volumes, mechanical ventilation, postnatal sepsis, and postnatal corticosteroids. Accordingly, it is possible to develop BPD without having RDS, but BPD absolutely can occur in preterm infants who developed and were treated for RDS. (40) Other complications of RDS in the preterm infant include IVH, patent ductus arteriosus, sepsis, and pulmonary hemorrhage, which likely result from a combination of prematurity, RDS, and its treatments.

Complications from the treatments for RDS are inevitable, but based on risk-to-benefit ratios of the treatments, the complications are mostly tolerable. Antenatal steroids do not have true short-term complications when examined in meta-analyses; there has been no associated increase in maternal death, maternal infection, fetal death, neonatal CLD, or neonatal birthweight. (1) Concerns of decreased birthweight (15) as well as trends toward increased incidence of IVH and long-term adverse behaviors have been voiced with the use of multiple repeat doses of antenatal steroids, but never consistently proven. (16) Interestingly, in a 30-year follow-up of infants who received antenatal corticosteroids, no change in adult size or blood lipid or cortisol concentrations was doumented, but there was a slight increase in the incidence of insulin resistance. (13) These results may have implications for the hypothesis of the fetal origins of adult disease. (1)

Mild complications of surfactant administration may include transient oxygen desaturation, apnea, and bradycardia, but such complications typically improve rapidly. (5) More serious complications include endotracheal tube blockage and pulmonary hemorrhage. (5) After administration, surfactant may distribute unevenly to only one lung or certain lobes. A second dose generally follows the same course as the first, which can lead to continued atelectasis of certain areas of the lungs. (9) As mentioned, natural surfactant administration causes an increase in grade 1 and 2 IVH compared with synthetic surfactant. (20) Finally, after surfactant administration, the clinical signs of a PDA may develop earlier in the clinical course. (17)

Complications of mechanical ventilation are not specific to infants being treated for RDS. Air leak syn-

dromes, including PIE and pneumothorax, are more common when the poorly compliant lungs in RDS are mechanically ventilated. (2) Pneumothorax is also associated with the use of nCPAP. (29)

Long-term Prognosis

Survival of infants who have RDS has improved greatly with the use of antenatal steroids and SRT. Preliminary data in infants treated with antenatal steroids suggest the possibility of less neurodevelopmental delay. (1) Overall, however, information regarding neurodevelopmental outcomes in the preterm infants treated for RDS is lacking, and long-term follow-up studies are needed.

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the pathophysiology and risk factors for RDS.
- Recognize the clinical, imaging, and laboratory features of RDS.
- Recognize the pathologic features of RDS.
- Know the clinical strategies and therapies used to decrease the risk and severity of RDS.
- Know the management of RDS, including surfactant replacement.

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NeoReviews Quiz

10. Normal lung development during fetal life occurs through a series of sequential phases that leads to a mature lung with a large surface area and a minimal diffusion distance for gas exchange. Of the following, the presence of respiratory bronchioles, alveolar ducts, and primitive alveoli in the developing lung is *most* characteristic of the:

    A. Alveolar phase.
    B. Canalicular phase.
    C. Embryonic phase.
    D. Pseudoglandular phase.
    E. Saccular phase.

11. In addition to phospholipids, pulmonary surfactant contains four major proteins: surfactant protein (SP)-A, SP-B, SP-C, and SP-D. Each surfactant protein has a specific function. Of the following, SP-B is *most* important for:

    A. Facilitating formation of tubular myelin.
    B. Participating in host innate immune defense.
    C. Promoting adsorption and spreading of surfactant.
    D. Regulating surfactant reuptake and recycling.
    E. Regulating surfactant secretion and uptake.

12. Surfactant replacement therapy has been approved by the United States Food and Drug Administration for the treatment of respiratory distress syndrome (RDS) since 1990. Several other therapeutic approaches have been studied as possible adjunct treatments for RDS, as reviewed in meta-analyses published in the *Cochrane Database of Systematic Reviews*. Of the following, the *most* promising adjunct treatment for RDS in preterm infants is the administration of:

    A. Antithrombin.
    B. Digoxin.
    C. Furosemide.
    D. Inositol.
    E. Thyroxin.

The reader is encouraged to write possible diagnoses for each case before turning to the discussion. We invite readers to contribute case presentations and discussions. Please inquire first by contacting Dr. Philip at aphilip@stanford.edu.

Author Disclosure

Drs Moussa and Smyth have disclosed no financial relationships relevant to this case. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Case Presentation

A newborn boy is admitted to the neonatal intensive care unit (NICU) because of pallor and respiratory distress. His mother is a 32-year-old primigravida, who has type 2 diabetes mellitus and whose prepregnancy treatment with metformin was changed to insulin early in the pregnancy. In the first trimester, the mother had a throat infection that was treated with clarithromycin. Results of routine antenatal serologic screening, ultrasonography, and fetal echocardiography were normal.

The mother presented to hospital with decreased fetal movements at 36 weeks and 3 days of gestation. Electronic fetal heart rate monitoring (EFM) was performed (Fig. 1) and she returned home. Several hours later, after review of the EFM record, she was recalled but could not be reached until the next morning, when EFM was repeated (Fig. 2).

A pale and nonvigorous male baby, who had a heart rate of 80 beats/min, was delivered by urgent cesarean section. He was resuscitated with bag-and-mask ventilation for 60 seconds followed by 100% free-flow oxygen; oxygen saturation was 75% at 3 minutes. His birthweight was 2.6 kg, his Apgar scores were 5 at 1 minute and 6 at 5 minutes, and his umbilical venous pH was 7.20.

On admission to the NICU, the infant's physical examination shows extreme pallor, tachypnea, mild-to-moderate subcostal retractions, nasal flaring, and intermittent grunting. His oxygen saturation is 92% on nasal continuous positive airway pressure of 5 cm H_2O and FiO_2 of 0.35. Pulmonary and cardiac auscultation yield normal results. His pulse is weak and capillary refill time is 4 seconds. His heart rate is 200 beats/min and oscillometric blood pressure cannot be obtained. His liver and spleen are not palpably enlarged. Neurologically, he is alert but irritable, he has normal muscle tone, he moves all limbs normally, and anterior fontanelle tension is normal. Laboratory investigations reveal the diagnosis.

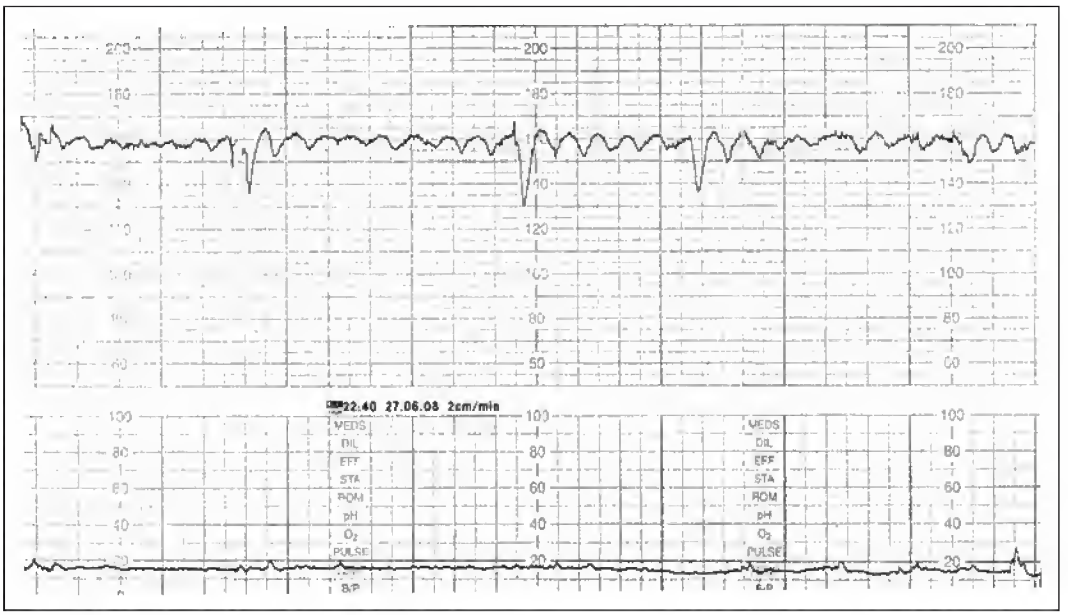

Figure 1. Initial electronic fetal heart rate monitoring strip.

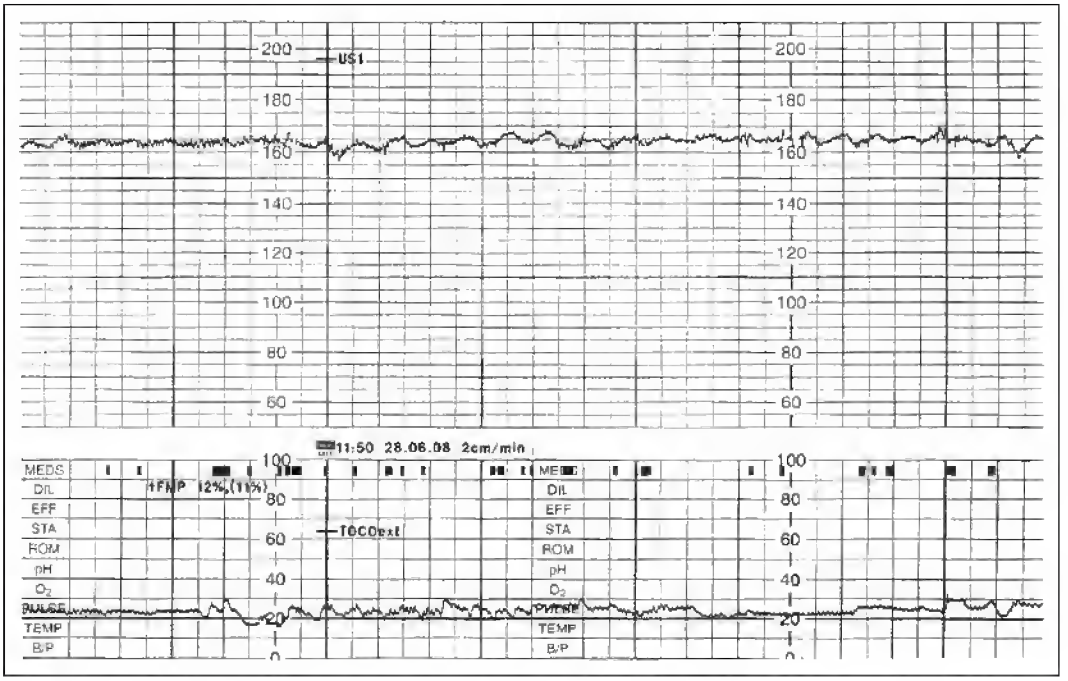

Figure 2. Second electronic fetal heart monitoring strip.

Case Discussion

The infant's hemoglobin was 2.9 g/dL (29 g/L). Group O, Rh-negative, packed red blood cells (PRBCs) were requested and two intravenous boluses of normal saline, each 10 mL/kg over 15 minutes, were administered while awaiting PRBCs. Umbilical venous and arterial catheters were inserted. The mean arterial pressure ranged from 44 to 53 mm Hg. Following a transfusion of group O Rh-negative PRBCs (20 mL/kg over 30 minutes), the hemoglobin increased to 7.7 g/dL (77 g/L). A further transfusion of 20 mL/kg cross-matched PRBCs was administered over 2 hours. Following these therapies, the hemoglobin was 12.7 g/dL (127 g/L), the heart rate was 150 beats/min, and perfusion had improved.

The initial arterial blood gas results were: pH of 7.09, Po_2 of 45 mm Hg, and base deficit 16.3 mEq/L. Arterial lactate was 88.8 mg/dL (9.86 mmol/L). There was no evidence of renal or hepatic injury that might have resulted from hypovolemic shock. A Kleihauer-Betke test on maternal blood was strongly positive for fetal red cells, indicating a fetomaternal hemorrhage (FMH) of approximately 200 to 230 mL. Magnetic resonance imaging of the infant's brain at 72 hours was read as normal. The infant's discharge examination on day 7 yielded normal results. On follow-up at 9 months of age, the infant was doing well and had reached the appropriate milestones for his age.

The clinical presentation was of anemia and hypovolemic shock. The sinusoidal electronic fetal heart rate pattern 12 hours prior to delivery was highly suggestive of fetal anemia. The causes of anemia in a newborn include a broad number of conditions (Table), but the positive Kleihauer-Betke test confirmed the diagnosis of FMH as the cause of anemia in this patient.

Table. Causes of Anemia in Newborns

Hemorrhagic Anemia
• Fetal hemorrhage
Spontaneous fetomaternal hemorrhage
Hemorrhage following amniocentesis
Twin–twin transfusion
Nuchal cord
• Placental hemorrhage
Placenta previa
Abruptio placentae
Multilobed placenta (vasa previa)
Velamentous insertion of cord
Placental incision during cesarean section
• Umbilical cord bleeding
Rupture of umbilical cord with precipitous delivery
Rupture of short or entangled cord
• Postpartum hemorrhage
Bleeding from the umbilicus
Cephalhematomas, scalp hemorrhages
Hepatic rupture, splenic rupture
Retroperitoneal hemorrhages
Hemolytic Anemia
• Immune disorders
Isoimmune: Rh and ABO incompatibility
Maternal immune disease: autoimmune hemolytic anemia, systemic lupus erythematosus
Drug-induced: penicillin
• Acquired red blood cell disorders
Infection: cytomegalovirus, toxoplasmosis, syphilis, bacterial sepsis
Disseminated and localized intravascular coagulation, respiratory distress syndrome
• Hereditary red blood cell disorders
Membrane defects: hereditary spherocytosis, hereditary elliptocytosis
Enzyme abnormalities: glucose-6-phosphate dehydrogenase, pyruvate kinase
Hemoglobinopathies: alpha-thalassemia syndromes, gamma/beta-thalassemia
Aplastic Anemia
• Blackfan-Diamond anemia

Data from Mentzer W, Glader B. Erythrocyte disorders of infancy. In: Taeusch W, Ballard R, Gleason C, eds. *Avery's Diseases of the Newborn*. 8th ed. Philadelphia, Pa: Elsevier Saunders; 2005:1180.

The Condition

FMH is defined as the passage of fetal red blood cells (RBCs) into the maternal circulation. Such passage occurs in 40% to 50% of all pregnancies but in minute amounts. (1) The exact pathophysiology is unknown. Massive FMH of more than 80 mL may occur in 1 in 1,146 pregnancies and transfusions of more than 150 mL in 1 in 2,813 pregnancies. (2) FMH can occur at any time in pregnancy but most often during the third trimester and during labor. (3) Most cases are of unknown cause, although cases have been associated

with abruptio placentae, vasa previa, chorioangioma, choriocarcinoma, thrombus of the umbilical vein, trauma, amniocentesis, and external cephalic version. (4)

FMH can occur acutely or chronically throughout the pregnancy. The degree and acuity of the hemorrhage determines the clinical presentation of the fetus or newborn and affects the prognosis. In the chronic form, which involves slower blood loss, the infant can present with severe anemia but have minimal symptoms or be asymptomatic. In acute cases, the infant may exhibit hydrops or be stillborn. The mother often presents with a history of decreased or absent fetal movements. EFM shows signs of fetal distress, as in decreased heart rate variability, late decelerations, bradycardia, and sinusoidal heart rate pattern. The sinusoidal fetal heart rate, first described by Modanlou and Freeman in 1982, is believed to be pathognomic of fetal anemia. The newborn can present with signs of anemia (pallor and tachycardia), hypovolemic shock, or even asphyxia. (1)(3)(4)

There are no large follow-up studies of infants who suffered from FMH, and the small studies have only had follow-up until the age of 1 year. However, case reports confirm that, in cases of a massive FMH, the child can develop a stroke or periventricular leukomalacia, which can lead to cerebral palsy. (4)

If FMH is diagnosed before birth, management depends on the gestational age. After 34 weeks of gestation, delivery is recommended if signs of fetal anemia or acute fetal distress are present. Before 34 weeks of gestation, the options vary according to the severity of the FMH. In mild cases, very careful serial monitoring or in utero transfusion are possible; intrauterine transfusion or the delivery of the fetus may be indicated in severe cases. (3)(5)

The Kleihauer-Betke test is the recommended test to detect FMH in cases of unexplained fetal distress, fetal death, or neonatal anemia. The test uses acid elution of maternal cells and the subsequent staining of fetal cells. Maternal erythrocytes are ruptured and appear as ghost cells, whereas the fetal RBCs stain strongly because of the stability of the fetal hemoglobin in an acid medium. (6) The fetal RBCs are counted as a proportion of the adult RBCs, and a quantitative estimate of the blood transfused from fetus to mother is determined using a formula. (7) One fetal RBC per 1,000 adult RBCs corresponds to a transfusion of about 5 mL of fetal blood into the mother's circulation. (3)

The test lacks some accuracy because maternal fetal hemoglobin increases during pregnancy. Also, it can present false-positive results in mothers who have hematologic conditions that increase hemoglobin F concentrations (thalassemia, sickle cell anemia). It can present false-negative results in situations where there is ABO incompatibility and where the fetus has received intrauterine transfusion. (4)

Some other tests can detect FMH, including the rosette test, micro D^u test, gel agglutination, and flow cytometry. However, these tests are only useful when the mother is Rh-negative and the fetus is Rh-positive because they depend on detection of RhD-positive RBCs. Only the flow cytometry test gives a quantitative result. Alpha-fetoprotein measurement in the mother has been shown to correlate with FMH. However, this test can yield false-positive results in many fetal conditions. Fluorescence in situ hybridization and DNA amplification currently is used as a research tool but is promising as an extremely sensitive tool. (6)

Lessons for the Clinician

In the presence of a history of decreased fetal movements accompanied by EFM showing a sinusoidal fetal heart rate, the clinician should prepare for resuscitation of an anemic infant and order group O Rh-negative blood for the delivery. A Kleihauer-Betke test should be ordered for the mother in any case of fetal death, anemia, or distress of unknown cause. Volume resuscitation with PRBCs should be performed promptly in an infant who has hypovolemic shock due to acute blood loss. Finally, it is important to diagnose FMH because it can have important repercussions on the infant's future neurodevelopment. (*Ahmed Moussa, MD, John Smyth, MD, Women's and Children's Health Centre of British Columbia, Division of Neonatology, University of British Columbia, Vancouver, British Columbia, Canada*)

American Board of Pediatrics Neonatal-Perinatal Medicine Content Specifications

- Know the causes and pathophysiology of acute fetal and neonatal blood loss.
- Know the clinical and laboratory findings and management of acute fetal and neonatal blood loss.

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1. Siemer J, Wendler A, Schild RL, Grab D. Massive fetomaternal hemorrhage and severe anemia in the newborn - two case reports. *Ultraschall Med.* 2008 December 12, epub ahead of print

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7. Mollison PL, Engelfriet CP, Contreras M. *Blood Transfusion in Clinical Medicine*. 10th ed. Oxford, England; Malden, Mass: Blackwell Science; 1997

Strip of the Month: July 2009

Maurice L. Druzin, MD,*
Nancy Peterson, RNC, PNNP, MSN, IBLC†

Author Disclosure
Dr Druzen and Ms Peterson have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Electronic Fetal Monitoring Case Review Series

Electronic fetal monitoring (EFM) is a popular technology used to establish fetal well-being. Despite its widespread use, terminology used to describe patterns seen on the monitor has not been consistent until recently. In 1997, the National Institute of Child Health and Human Development (NICHD) Research Planning Workshop published guidelines for interpretation of fetal tracings. This publication was the culmination of 2 years of work by a panel of experts in the field of fetal monitoring and was endorsed in 2005 by both the American College of Obstetricians and Gynecologists (ACOG) and the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN). In 2008, ACOG, NICHD, and the Society for Maternal-Fetal Medicine reviewed and updated the definitions for fetal heart rate patterns, interpretation ,and research recommendations. Following is a summary of the terminology definitions and assumptions found in the 2008 NICHD workshop report. Normal values for arterial umbilical cord gas values and indications of acidosis are defined in Table 1.

Assumptions from the NICHD Workshop

- Definitions are developed for visual interpretation, assuming that both the fetal heart rate (FHR) and uterine activity recordings are of adequate quality
- Definitions apply to tracings generated by internal or external monitoring devices
- Periodic patterns are differentiated based on waveform, abrupt or gradual (eg, late decelerations have a gradual onset and variable decelerations have an abrupt onset)
- Long- and short-term variability are evaluated visually as a unit
- Gestational age of the fetus is considered when evaluating patterns
- Components of fetal heart rate FHR do not occur alone and generally evolve over time

Definitions

Baseline Fetal Heart Rate

- Approximate mean FHR rounded to increments of 5 beats/min in a 10-minute segment of tracing, excluding accelerations and decelerations, periods of marked variability, and segments of baseline that differ by >25 beats/min
- In the 10-minute segment, the minimum baseline duration must be at least 2 minutes (not necessarily contiguous) or the baseline for that segment is indeterminate
- Bradycardia is a baseline of <110 beats/min; tachycardia is a baseline of >160 beats/min
- Sinusoidal baseline has a smooth sine wave-like undulating pattern, with waves having regular frequency and amplitude

Baseline Variability

- Fluctuations in the baseline FHR of two cycles per minute or greater, fluctuations are irregular in amplitude and frequency, fluctuations are visually quantitated as the amplitude of the peak to trough in beats per minute
- Classification of variability:
  - Absent: Amplitude range is undetectable
  - Minimal: Amplitude range is greater than undetectable to 5 beats/min
  - Moderate: Amplitude range is 6 to 25 beats/min
  - Marked: Amplitude range is >25 beats/min

*Charles B. and Ann L. Johnson Professor of Obstetrics; Chief, Division of Maternal-Fetal Medicine; Co-Medical Director, Mid-Coastal California Perinatal Outreach Program, Stanford University School of Medicine, Palo Alto, Calif.
†Director of Perinatal Outreach, Stanford University, Palo Alto, Calif.

Table 1. **Arterial Umbilical Cord Gas Values**

	pH	Pco_2 (mm Hg)	Po_2 (mm Hg)	Base Excess (mEq/L)
Normal*	≥7.20 (7.15 to 7.38)	<60 (35 to 70)	≥20	≤−10 (−2.0 to −9.0)
Respiratory Acidosis	<7.20	>60	Variable	≤−10
Metabolic Acidosis	<7.20	<60	Variable	≥−10
Mixed Acidosis	<7.20	>60	Variable	≥−10

*Normal ranges from *Obstet Gynecol Clin North Am.* 1999;26:695

Accelerations

- Abrupt increase in FHR above the most recently determined baseline
- Onset to peak of acceleration is <30 seconds, acme is ≥15 beats/min above the most recently determined baseline and lasts ≥15 seconds but <2 minutes
- Before 32 weeks' gestation, accelerations are defined by an acme ≥10 beats/min above the most recently determined baseline for ≥10 seconds
- Prolonged acceleration lasts ≥2 minutes but <10 minutes

Late Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring after the peak of uterine contractions
- Considered a periodic pattern because it occurs with uterine contractions

Early Decelerations

- Gradual decrease in FHR (onset to nadir ≥30 seconds) below the most recently determined baseline, with nadir occurring coincident with uterine contraction
- Also considered a periodic pattern

Variable Decelerations

- Abrupt decrease in FHR (onset to nadir <30 seconds)
- Decrease is ≥15 beats/min below the most recently determined baseline lasting ≥15 seconds but <2 minutes
- May be episodic (occurs without a contraction) or periodic

Prolonged Decelerations

- Decrease in the FHR ≥15 beats/min below the most recently determined baseline lasting ≥2 minutes but <10 minutes from onset to return to baseline

Decelerations are tentatively called recurrent if they occur with ≥50% of uterine contractions in a 20-minute period.

Decelerations occurring with <50% of uterine contractions in a 20-minute segment are intermittent.

Sinusoidal Fetal Heart Rate Pattern

- Visually apparent, smooth sine wavelike undulating pattern in the baseline with a cycle frequency of 3 to 5/minute that persists for ≥20 minutes.

Uterine Contractions

- Quantified as the number of contractions in a 10-minute window, averaged over 30 minutes. Normal: ≤5 contractions in 10 minutes Tachysystole: >5 contractions in 10 minutes

Interpretation

A three-tier Fetal Heart Rate Interpretation system has been recommended as follows:

- Category I FHR tracings: Normal, strongly predictive of normal fetal acid-base status and require routine care. These tracings include all of the following:
  - Baseline rate: 110 to 160 beats/min
  - Baseline FHR variability: Moderate
  - Late or variable decelerations: Absent
  - Early decelerations: Present or absent
  - Accelerations: Present or absent
- Category II FHR tracings: Indeterminate, require evaluation and continued surveillance and reevaluation. Examples of these tracings include any of the following:
  - Bradycardia not accompanied by absent variability
  - Tachycardia
  - Minimal or marked baseline variability
  - Absent variability without recurrent decelerations
  - Absence of induced accelerations after fetal stimulation
  - Recurrent variable decelerations with minimal or moderate variability

  - Prolonged decelerations
  - Recurrent late decelerations with moderate variability
  - Variable decelerations with other characteristics, such as slow return to baseline
- Category III FHR tracings: Abnormal, predictive of abnormal fetal acid-base status and require prompt intervention. These tracings include:
  - Absent variability with any of the following:
    - Recurrent late decelerations
    - Recurrent variable decelerations
    - Bradycardia
  - Sinusoidal pattern

Data from Macones GA, Hankins GDV, Spong CY, Hauth J, Moore T. The 2008 National Institute of Child Health and Human Development workshop report on electronic fetal monitoring. *Obstet Gynecocol.* 2008;112: 661–666.

We encourage readers to examine each strip in the case presentation and make a personal interpretation of the findings before advancing to the expert interpretation provided.

Case Presentation

History

A 27-year-old G1 P0000 woman presents to her doctor's office at 32–5/7 weeks' gestation complaining of decreased fetal movement for the past 24 hours. Fetal monitoring in the office reveals a prolonged deceleration followed by an apparent sinusoidal pattern. The patient and her husband are sent immediately to the perinatal diagnostic center for a biophysical profile. The profile score is 2/10, which is associated with fetal compromise. In addition, Doppler studies show an increase in the peak velocity of systolic blood flow in the middle cerebral artery, which is consistent with fetal anemia. The prenatal course was normal up to this point and the past medical history was negative. The woman is transferred to labor and delivery for further evaluation and preparation for a cesarean section. On arrival to labor and delivery, EFM is begun (Fig. 1), and appropriate laboratory tests for surgery are ordered.

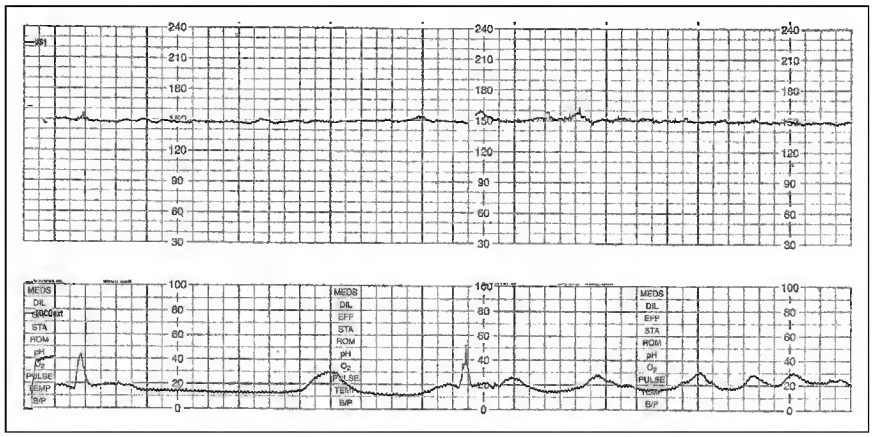

Figure 1. EFM Strip #1.

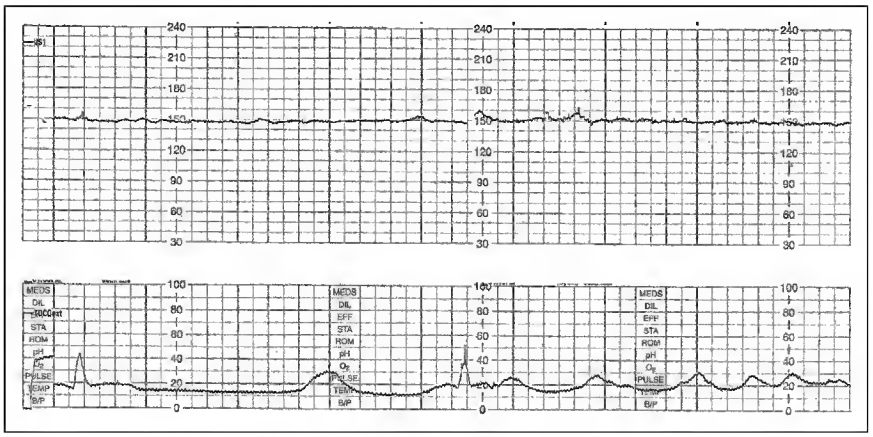

Figure 1. EFM Strip #1.

Findings on EFM Strip #1 are:

- Variability: Minimal
- Baseline Rate: 150 beats/min
- Episodic Pattern: None
- Periodic Pattern: None noted
- Uterine Contractions: Low-amplitude, frequent contractions
- Interpretation: Category II: Indeterminate, which means that it is not predictive of abnormal fetal acid-base status
- Differential Diagnosis: Fetal anemia possibly due to a placental abruption, fetal maternal hemorrhage, ruptured vasa previa, or hemolytic anemia
- Action: The goal is to optimize blood flow to the uterus and improve oxygenation to the fetus. Potential interventions include maintaining continuous fetal monitoring, placing the mother in a lateral position, administering an intravenous bolus of lactated Ringer solution, and administering 100% oxygen per nonrebreather mask. Even though the baseline rate is within the normal range, the minimal variability and the biophysical score of 2/10 are very concerning. Loss of variability is more predictive of hypoxemia and acidemia in a preterm fetus compared with a term fetus. A preterm fetus also can progress much faster from a reassuring to nonreassuring FHR status than a term fetus (Freeman et al, 2003). A Kleihauer-Betke blood test is ordered to determine if fetal hemoglobin cells are present in the maternal bloodstream.

The noted actions are taken, and an immediate tracing is obtained (Fig. 2).

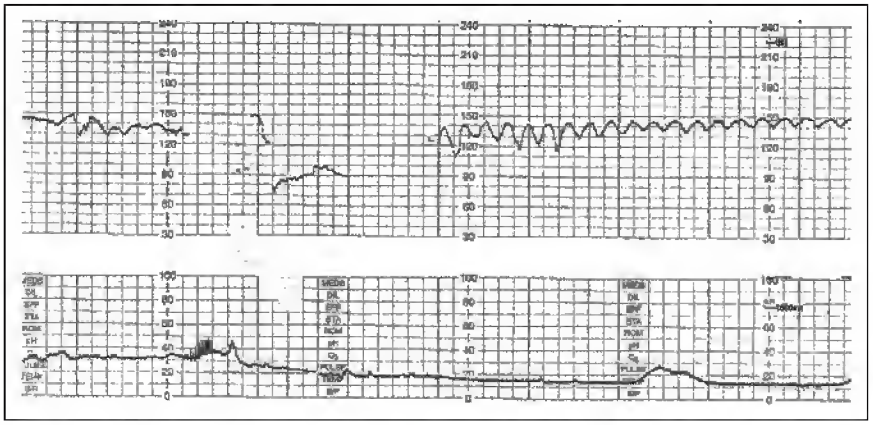

Figure 2. EFM Strip #2.

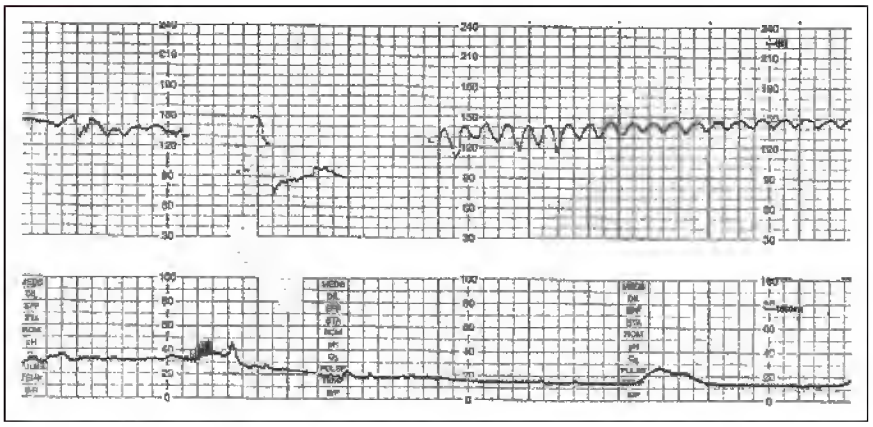

Figure 2. EFM Strip #2.

Findings on EFM Strip #2 are:

- Variability: Initially moderate, then indeterminant
- Baseline Rate: Initially 135 beats/min, then unable to determine due to development of a sinusoidal pattern
- Episodic Pattern: Appears to be a deceleration but due to a 3-minute gap of missing data in the tracing, the type of deceleration cannot be determined
- Periodic Pattern: None noted
- Uterine Contractions: Irregular and mild by palpation
- Interpretation: A sinusoidal pattern would be classified as a Category III FHR tracing, which means that it is predictive of abnormal fetal acid-base status at the time of observation
- Differential Diagnosis: Fetal anemia of unknown cause. However, the presence of decreased fetal movement in conjunction with a sinusoidal pattern suggests that a fetomaternal hemorrhage may be the cause. In addition to fetal anemia, a true sinusoidal pattern is associated with hypoxia/asphyxia, fetal infection, and fetal cardiac anomalies. Whatever the pathology, a true sinusoidal pattern is a significant finding that implies fetal decompensation and requires immediate intervention.
- Action: Proceed with plans to deliver the baby. Notify the neonatal intensive care staff and neonatologist of fetal status. Continue with all of the previous interventions.

The Kleihauer-Betke test is positive for fetal cells in the maternal bloodstream, which confirms a fetomaternal hemorrhage. Thirty minutes later, another tracing is obtained (Fig. 3).

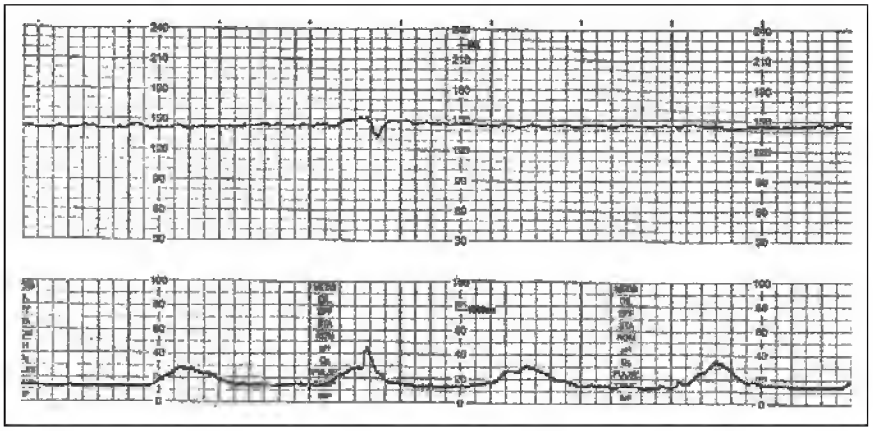

Figure 3. EFM Strip #3.

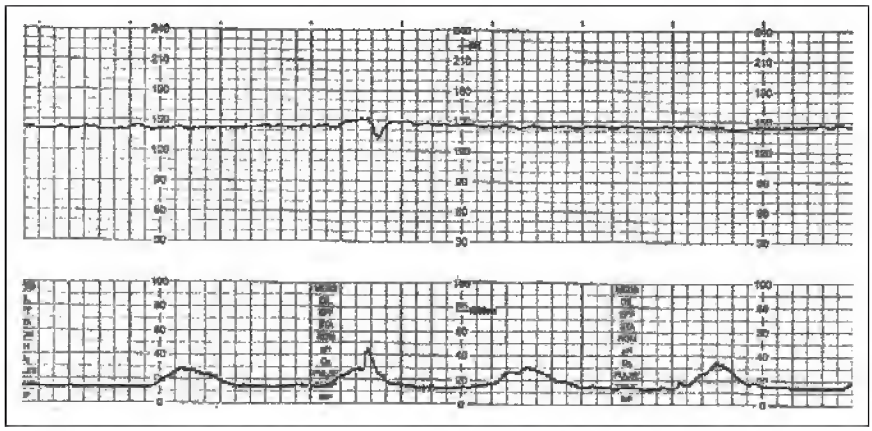

Figure 3. EFM Strip #3.

Findings on EFM Strip #3 are:

- Variability: Minimal
- Baseline Rate: 145 beats/min
- Episodic Pattern: None noted
- Periodic Pattern: None noted
- Uterine Contractions: Every 2 minutes, lasting 40 to 60 seconds. Intensity and resting tone are obtained per palpation
- Interpretation: Category II FHR
- Actions: Despite the disappearance of the sinusoidal pattern and the presence of a normal baseline FHR, the continued minimal variability and concerning findings on diagnostic tests warrant an immediate delivery.

Outcome

Forty-five minutes later, a pale viable male infant weighing 1,673 g is delivered by cesarean section. Apgar scores are 8 at 1 and 5 minutes. The baby is sent to the neonatal intensive care unit, where neonatal anemia is diagnosed. He ultimately does well. Pathologic examination of the placenta reveals numerous focal infarctions. A specimen for cord gases was drawn but was not sufficient for testing.

Reference

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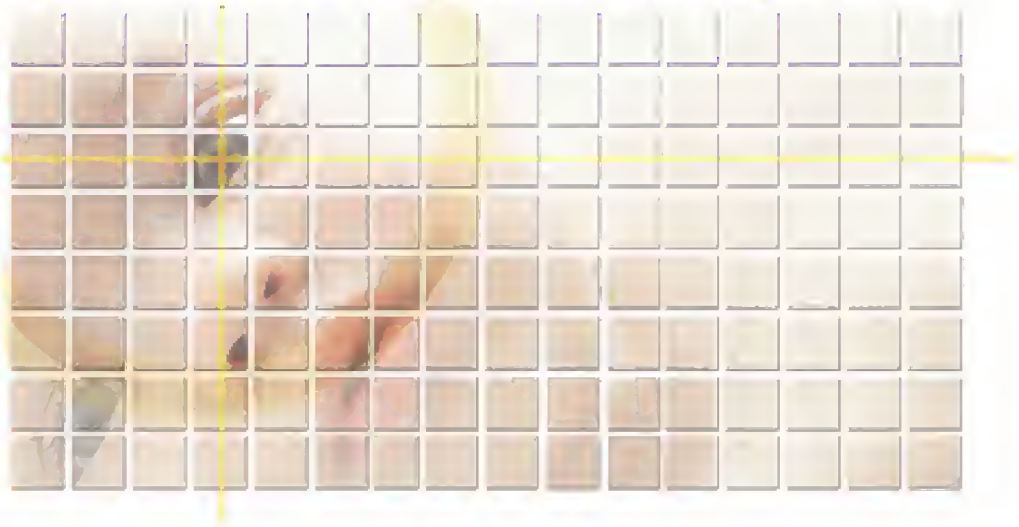

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The Case:

Large right-sided neck and chest mass in a newborn.

Figure 1

A term male newborn is transferred to neonatal intensive care unit a few hours after birth because of a huge cervicothoracic mass.

Prenatal History:

- 31-year old G2p1Ab0 mother
- Prenatal laboratory evaluation: blood group A-positive, hepatitis B surface antigen-negative, and VDRL-negative
- The only medication used by the mother during pregnancy was prenatal multivitamins

Birth History:

- Term uncomplicated pregnancy
- Delivery by elective cesarean section due to detection of a cervicothoracic mass on prenatal ultrasonography
- Birthweight of 3,400 g
- Apgar scores of 8 and 9 at 1 and 5 minutes, respectively

There is no history of consanguinity between the parents, and another child is healthy.

Continue with case progression...

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Case Progression:

Physical Examination:

- Appropriate for gestational age infant
- Diminished Moro reflex on the right side
- Fixed, multilobulated, nontender mass on the right side of the cervical area measuring 20×7×10 cm and extending toward right side of the thoracic area; several ecchymotic areas and vascular patterns on the surface

Laboratory Evaluations:

- Complete blood count: Within normal limits
- Serum electrolytes, calcium, blood glucose, blood urea nitrogen, and creatinine: Within normal limits
- Liver function tests: Normal
- Coagulation panel: Within normal limits for age

Imaging Studies:

- Chest radiograph: Soft-tissue mass without calcification over right upper arm and neck
- Abdominal and pelvic ultrasonography: Normal
- Brain ultrasonography and computed tomography scan: Normal
- Cervicothoracic magnetic resonance imaging (MRI): Large T1-isotense mass on

the right side of cervical region extending toward the right thoracic wall

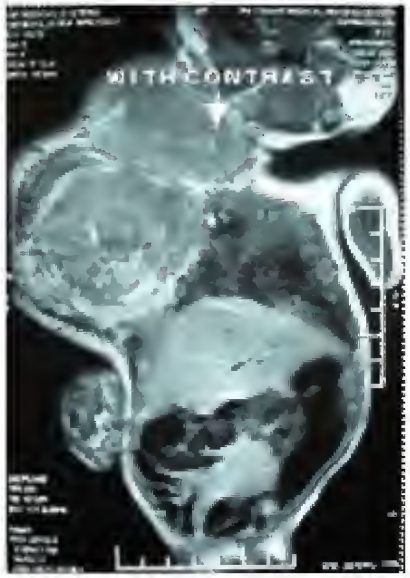


Figure 2

- Cervical Doppler ultrasonography: Large hypoechoic and heterogenous mass measuring 20 cm in its largest diameter, with hypervascular pattern and low-resistance arterial flow suggestive of hemangioma
- Cervical magnetic resonance angiography: Early opacification of venous system and sagital transverse sinuses, in favor of vascular malformation in the right upper chest and cervical region

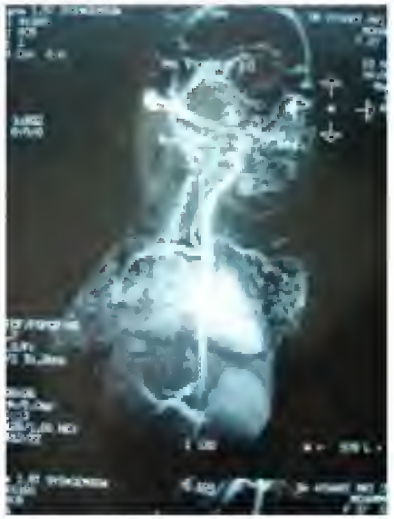
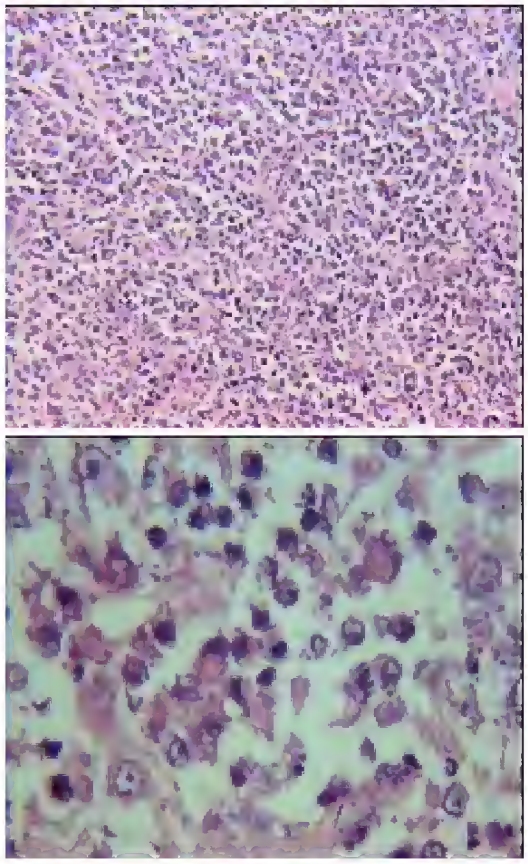


Figure 3

During the course of the hospitalization, while the patient was being evaluated, the mass grew rapidly, causing difficulty in breathing and swallowing. After surgical consultation, plans were made to remove the mass after stabilization of the infant. At surgery, the huge mass was found to be invading the local nerves and vessels. The mass was removed surgically and a specimen was sent for pathologic examination.

Pathologic Examination:

Diffuse proliferation of rounded cells with prominent eccentric nuclei and hyalinelike inclusion bodies in the cytoplasm. Immunoreactive for vimentin, cytokeratin, and epithelial membrane antigen.



Figures 4 & 5

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Differential Diagnosis:

Huge cervicothoracic mass in newborn:

- Hemangioma
- Lymphangioma
- Neuroectodermal tumor
- Neuroblastoma
- Lymphoma
- Rhabdomyosarcoma
- Rhabdoid tumor
- Extraskeletal sarcoma
- Cystic hygroma

Think first, then...go to the actual diagnosis.

Seeing Diagnosis in a whole new light

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Actual Diagnosis:

Malignant Rhabdoid Tumor (MRT)

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MRT is very rare in the neonatal period. This highly aggressive tumor of controversial origin initially was described in the kidney by Beckwith and Palmer in 1978 as a sarcomatous variant of Wilms tumor[1, 2]. MRT is fatal during the neonatal period[2]. Only five cases of extrarenal MRT have been reported during the neonatal period[1,3,4]. The tumor predominantly involves deep axial locations such as the neck or paraspinal region.

Review of a relatively large series of three independent studies of extrarenal MRT, consisting of 49 patients, revealed the following data: 25 females (51%) and 24 males (49%), with age ranges from 2 months to 56 years and a median age of 7.3 years[5]. Most cases were infants or children, and 28 patients (57%) were younger than 10 years of age. The tumors arose most frequently in deep, axial locations, including the neck and paravertebral regions. The detailed anatomic distribution of primary tumors was as follows: neck (12.2%), thigh (12.2%), abdominal cavity and retroperitoneum (10.2%), paraspinal region (8.2%), pelvic cavity (8.2%), chest wall (6.1%), and perineal region (4.1%).

MRTs have rapidly fatal clinical courses in most cases. The 5-year survival rate in the previously noted series was less than 20%; about 42% of patients died within 1 year of diagnosis.

A unique type of MRT is seen in soft tissue, in which the initial presentation is widely disseminated disease at birth or shortly thereafter and no demonstrable primary tumor in the kidney or brain. Known as "congenital disseminated malignant rhabdoid tumor,"[5] these tumors sometimes have placental metastases and are associated with a

rapidly deteriorating clinical course terminating in death.

Microscopically, MRT is composed of a diffuse proliferation of rounded or polygonal cells that have eccentric nuclei, prominent nucleoli, and glass eosinophilic cytoplasm containing hyalinelike inclusion bodies, arranged in sheets and nests. Such characteristic "rhabdoid cells" also are present in certain soft-tissue sarcomas such as synovial sarcoma and leiomyosarcoma. Both MRT of soft tissues and proximal type epithelioid sarcoma show immunoreactivity for vimentin, cytokeratin, and epithelial membrane antigen[5].

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